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**Nervous and Mental Disease Monograph Series No. 30**

# **The Internal Secretions** **AND THE** **Nervous System**

**By**

**DR. M. LAIGNEL-LAVASTINE**  
**OF PARIS**

**NERVOUS AND MENTAL DISEASE PUBLISHING COMPANY**  
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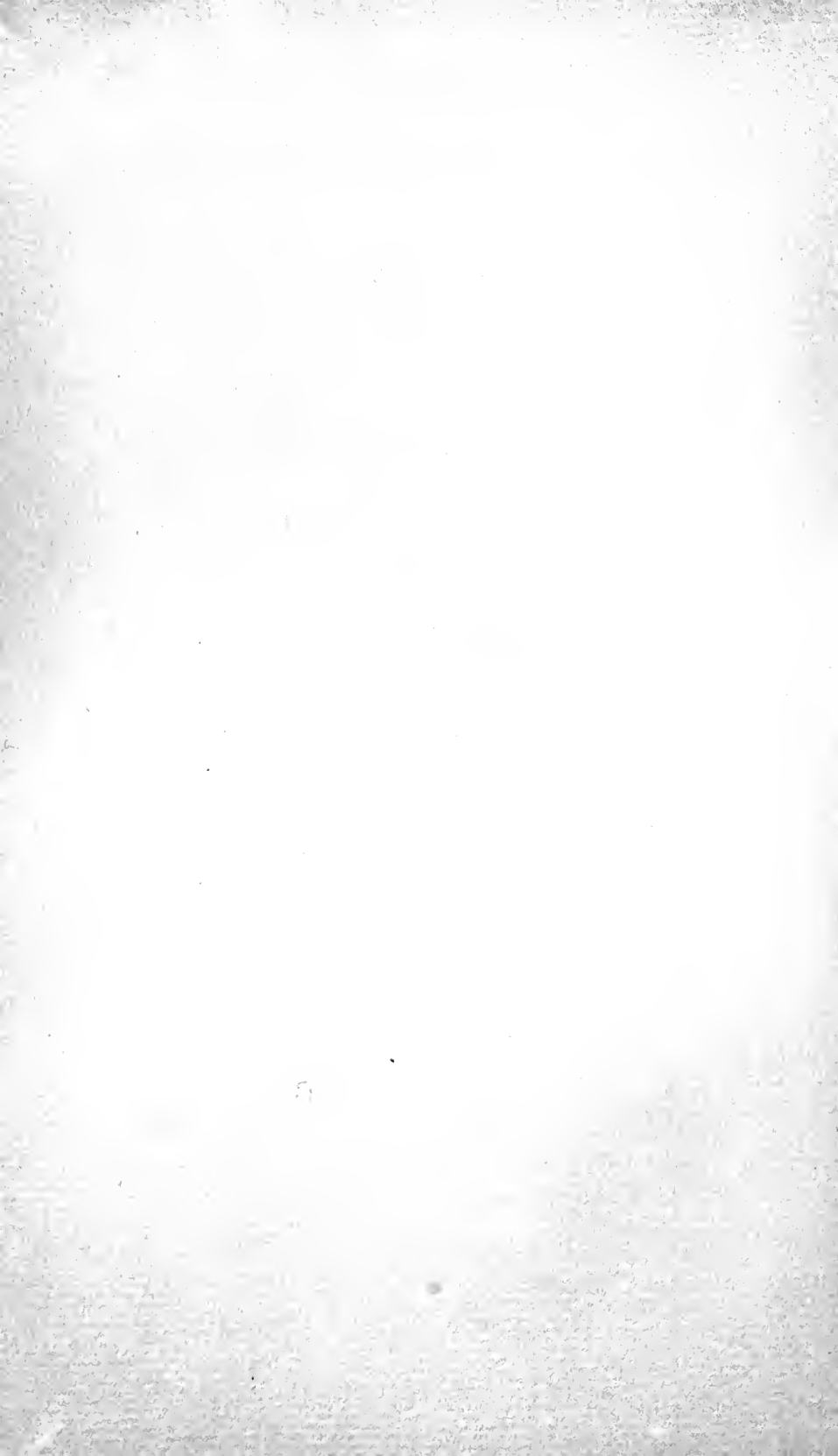
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## TRANSLATOR'S PREFACE

In the original French "The Internal Secretions and the Nervous System,"<sup>1</sup> by Prof. Laignel-Lavastine, is a classic. The translation is crude and without literary merit, and its only virtue is that a sincere attempt has been made to preserve its scientific value.

As proper innervation of the internal organs is necessary for health, and considering that there is an intimate relationship between the ductless glands and the nervous system, the proper understanding of the subject is not only of interest to the neurologist but to the general practitioner as well.

Organotherapy dates back to remote ages, as Dr. Diner has stated in his introduction. The Chinese treated obesity with preparations made from canine orchitic extracts and heart disease and epilepsy with dried and powdered frogs and newts. It has been shown by Abel's investigations that the skins of these animals contain an appreciable amount of adrenalin owing to the presence of cutaneous adrenals. To-day suprarenal extract is used in certain forms of heart disease and epilepsy with excellent results. Moreover we have no other adequate treatment for eunuchoid obesity than the administration of orchitic extracts. It would seem that modern medical knowledge is not the only healing art that was ever practiced. Empirics they were perhaps, but be that as it may "There were Kings before Agamemnon."

If the renewed interest in endocrinology has done nothing else for the art of medicine it has shown the utter futility of regarding physiology and pathology en masse. It is the individual and the study of the individual that is of supreme importance. Everyone has his own proper physiology and his own proper pathology as well. Following along their lines his life takes its course. That there are a broad common physiology and pathology none can deny, but that each individual has his own physiological and pathological variant is also not to be questioned. There is no truer saying than that "what is one man's meat is another man's poison," and it is the disregard of this fact that has hampered the advance of medical

<sup>1</sup> Article written in July, 1914, for the Congress at Berne, which did not take place on account of the War. I here publish the entire text, just as it was given to the Revue de Medecine in July, 1914.

diagnosis and therapeusis for years. Whether it comes under the heading of mechanistic physiology or vitalistic physiology it is the individual physiology that has to be carefully analyzed and considered before a proper appreciation of health and disease can be arrived at. Endocrinology has taught, and is still teaching us to analyze our cases by close clinical observation and research. In many ways Nature is a kind mistress after all, and even her misfits are frequently granted a *modus vivendi* which can only be appreciated by the right kind of clinical study. In the analysis of endocrinal disease a slipshod method is worse than useless. The family history, the previous history, the present history, the personal idiosyncrasies, likes and dislikes, physical make-up and appearance, in fact all that concerns the individual must be elicited, weighed and balanced even to the most minute detail. In this way alone can success be arrived at.

It would be presumptuous in me to enter into detailed descriptions of methods of endocrinological research which has been furthered by American observers. When the time is ripe for the publication of well-authenticated facts on the subject they will appear in proper form. I may be pardoned, however, in stating here certain conclusions which have been arrived at, and which have been confirmed time and time again.

*A.* Briefly stated the life of every individual is dominated largely if not wholly by his ductless gland chain.

*B.* Certain of these glands assume a preponderating influence on the morphology, physiology and pathology of the individual.

*C.* Certain tropisms are existent, so that we have the pituitary, thyroidal, adrenal, etc., type of individual.

*D.* Certain diseases, both of an acute and constitutional character, are welded, as it were, with the glandular tropisms, and belong to them, and are part of their distinctive pathology, either functional or organic. This is not only true of acromegaly, Basedow's disease or Addison's disease, but of many other diseases as well.

*E.* The glandular influence having so much to do with morphology, the physical make-up of the individual gives marked evidence of the glandular constellation under which he lives and has his being.

*F.* Within certain limits if the previous history of the individual be accurately known, his physical appearance can be approximately described, and his physiological and future pathological states can be predicted.

Some of these conclusions need no defense, and will be acceded to by all who have given the subject even a moment's consideration, while others will not be admitted by all endocrinologists.

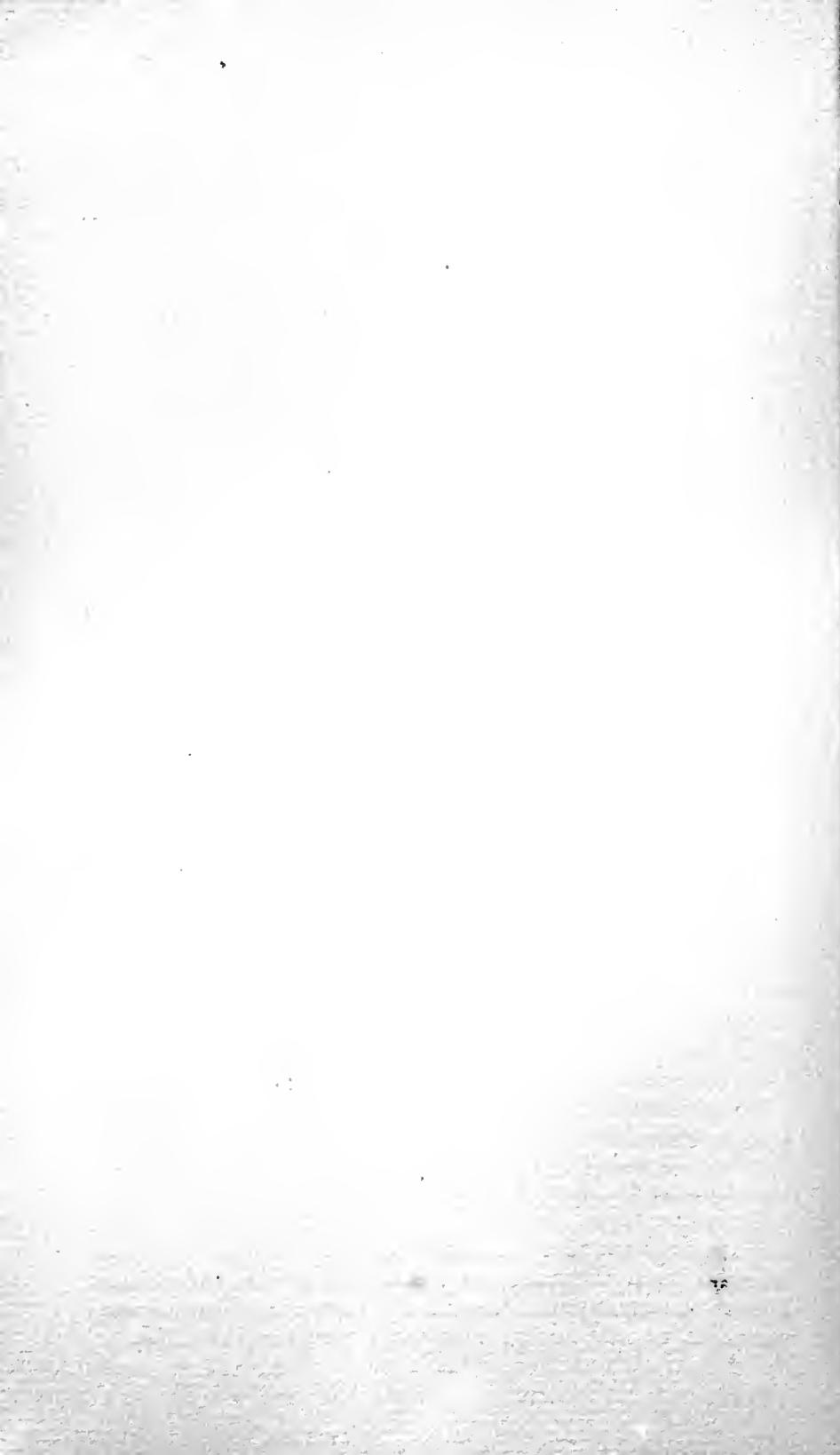
The results obtained in the experimental feeding of tadpoles are very significant. The small amphibia that were fed on thyroid gland developed into tiny frogs described as "*petit vieux*," and those that were fed on thymus grew into enormous tadpoles or "*grand enfants*." This experiment proves to some extent at least why taking two individuals of the same age, one may look like a premature old man, and the other have the appearance of unwarranted juvenility.

The physiology, psychology and pathology of the two will follow the thyroïdal and thymic influences that have had such a marked bearing on their morphology.

Take for example the dominion of the pituitary gland on certain types of body structure. Giantism in youth, acromegaly in adult life and shrinking in old age. There are small pituitary types as well. The dominating influence of the pituitary makes for feminism in the male, just as the dominating influence of the adrenals makes for masculinity in the female. The thyroïdal individual has his marked personal characteristics—his bright intelligent eye, his good clean teeth, his temperamental attitude toward life, his freedom from infectious disease except measles and typhoid and his tendency towards intestinal, certain forms of cardio-vascular and neurotic disturbances. The pituitary individual, easily recognized by his structural make-up, has his own peculiarities. He is musical, has an abnormally acute sense of rhythm and is prone to diseases attended by periodicity and to syphilis (Charcot joint—a local acromegaly). The adrenal individual has his strong masculinity, his tendency to hypertrichosis and pigmentosis, his liability to diphtheria, to hyperchlorhydria, to hypertension, to certain forms of pulmonary disease, to hernia and varicocele. These master types have their variants depending upon the influences of the other glands, especially marked in the gonads. The endocrine system has been well described as the ductless gland chain, and it is imperative to realize that every link counts. The clinical picture is never a simple one.

It will be through endocrinological study and investigation that we will come to a better understanding of humanity. We will see how within certain broad lines the life of the individual takes its course. We will understand perhaps what the world calls Fate.

F. T. ROBESON





## TRANSLATOR'S INTRODUCTION

*"Every man, from the highest to the lowest station, ought to warm his heart and animate his endeavors with the hope of being useful to the world, by advancing the art which is his lot to exercise; and for that end he must necessarily consider the whole extent of its application, and the whole weight of its importance."*—JOHNSON.

In making the writings of Laignet-Lavastine accessible to those not familiar with the French language, the translator has certainly hearkened to the admonition quoted above.

The importance of the internal secretions, both as etiological factors and as remedial agents, is being recognized more and more and anything which adds to our understanding of this highly complex subject should be welcomed with open arms by the medical profession.

Organotherapy or the use of animal matter in the treatment of disease is not by any means a new addition to the medical armamentarium. It is the intelligent interpretation of the symptom-complexes arising from dysfunction of the endocrine glands and the rational application of the secretions of these glands which anew engages the attention of the medical research worker and clinician alike.

The indirect application of animal tissues and organs to the treatment of disease finds its first expression at the sacrificial altar.

In gray antiquity, medicine and religion went hand in hand. God only could cure diseases and those of his representatives who were close to him in his service, the high priests, were empowered to execute his will in this direction as well as in religious matters. History records that as far back as 2000-3000 B.C. the treatment of disease was in the hands of the priests in Egypt. In Greece the Asclepiades, the priests of the temple of Asclepias, were entrusted with this important function. And Moses transferred to the priests the knowledge of medicine which he accumulated in Egypt.

The Hebrew literature, while replete with medical information, gives but scant evidence of animal therapy. No doubt the term "unclean" which is so frequently employed as a prohibitive injunction with reference to food, hygiene and other matters, comes into play here and accounts for the scant use of animal matter for medic-

inal purposes. In Joma, VIII, 6, we find that "One bitten by a mad dog was given the liver of the dog as an antidote" and the use of small doses of urine is passingly mentioned in another section, but whether to be taken internally or applied externally is not clearly stated.

However, if we cast our eye on the medical literature of other nations and peoples, we find no lack of evidences of animal therapy. Without making any attempt at chronological arrangement, I will merely cite a few instances.

The Papyrus Eberus recommends: human brain, half with honey and half dried, as a remedy against inflammation of the eyes. Dioscorides, first century of present era (II, 21), recommends the fried brain of the hare as a good remedy for the cure of "Tremor, Convulsions, etc." Sextus Platonius (330 A.D.) recommends the fried brain of the hare given internally to aid dentition in children. Celsus (II, 31, 34) as well as Plinius (XXVIII, 60) suggest the use of brain of the hare for urinary incontinence. And Plinius, Dioscorides and others advise the use of brain of different animals for the treatment and cure of epilepsy.

The liver also plays an important part in the *materia medica* of antiquity. Besides the quotation previously mentioned, we find that Hippocrates speaks of the benefit to be derived from the use of sheep's liver and of goat's liver in the treatment of diseases of the uterus. Plinius considers human liver as indicated to combat epilepsy; and Scribonius Largus uses "a piece of liver from a suffocated gladiator" for the same purpose (epilepsy).

Herophilus (300 B.C.) employs liver in cases of dysmenorrhea and metrorrhagia, as does Plinius, who also finds it useful against cough, tachycardia and ascites.

Bile is employed by Hippocrates in gynecological practice in the form of suppositories to combat sterility, prevent abortions and to ameliorate dysmenorrhea and amenorrhea. Plinius uses bile as a cathartic internally and applies it externally in treating diseases of the eye and to remove warts. Sextus Platonius treats dizziness, epilepsy and asthma by internal medication with bile. Orchitic substance is mentioned by Susruta (400-600 B.C.) for the treatment of obesity.

Particularly rich in information on the subject of organotherapy are the writing of Dioscorides. Thus we find that the blood of doves and wild hens is a valuable remedy against recent injuries of

the eyes, against hemorrhages and in many other pathological conditions. The blood of doves is especially valuable in hemorrhages of the brain, while the blood from other animals, such as goat, sheep, rabbit, etc., fried in a pan and taken internally, cures or stops dysentery. Blood from land-turtles is a sure cure for epilepsy. Menstrual blood prevents conception when painted in a circle around the body (abdomen?) or if one steps over it (blood). When rubbed in as a liniment it removes podagra and roseola. Feces of different animals also finds manifold uses. So for instances it is indicated to reduce inflammations, remove scrophula and gland-enlargements, correct prolapsus uteri, chase away mosquitoes, aid menstruation and to promote abortion.

Frogs prepared with oil and salt are a sure antidote for serpent's bite. Incidentally they cure painful tendons and stop bleeding when applied externally after burning and powdering them.

Testicle, dried and finely powdered, taken in wine is also used as antidote for serpents' bites but the beaver's testicle is especially valuable to help in bringing on the menstrual flow, aid abortion and promote expulsion of retained placenta. Incidentally it also finds its use in relieving cramps, convulsions and nervousness. Crabs, especially river-crabs, when boiled with honey are recommended for the removal of carcinomatous growths, and when boiled with meat-soup are indicated in the treatment of phthisis pulmonalis. Sea-crabs may be used for the same purposes but are less efficient. Lungs, especially fox's lungs, dried and taken internally cure asthma. And finally Dioscorides recommends urine for a number of diseases. So for instance is one's own urine good against serpents' bites; that from a mad dog against the bite of the dog, while the urine of an innocent boy, taken internally, cures orthopnea. Urine is also employed in various forms against eruptions, dysmenorrhea, pains in uterus, earache and urinary calculus.

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## AUTHOR'S INTRODUCTION

The relations of the internal secretions and the nervous system constitute an immense subject, which requires to be classified and condensed in as short a report as this to escape the penalty of remaining under vague generalities.

The most recent and important work issued on this question is the second edition of the remarkable production of Professor Arthur Biedl, "*Innere Sekretion, ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie.*" It contains, perfectly classified, all that has appeared of interest on the internal secretions up to the year 1913.<sup>2</sup> The physiological researches and experiments are herein particularly well set forth.

As I have the honor and the pleasure of having Professor Biedl himself as co-reporter, I would show poor taste in not leaving it to him to demonstrate the physiological part of the question.

I shall limit myself then to the pathological part. From a pathological standpoint the relations of the internal secretions and the nervous system are far from being completely cleared up, as one may gather from the recent reports of N. Pende,<sup>3</sup> G. Ghedini<sup>4</sup> and Parhon<sup>5</sup> at the congress of 1912 and 1913, and I have no hesitancy in stating with the Philalèthe of the Philosophical Dialogues of Renan: "For my part I am accustomed to classify my ideas on the subject in three categories. The first, unfortunately very limited, is that of the certainties; the second is that of the probabilities; the third is that of dreams. We will refrain from mentioning the last if you please, Euthyphron, as in all probability it exists for each one of us as the dearest part of all."

In fact, since my report of 1908 at the Congress of Dijon, on

<sup>2</sup> I refer here for the bibliography, also to the recent volume of Pr. Gley, *Les Secretions internes*, Baillière, 1914.

<sup>3</sup> N. Pende, *Les secrét. int. en rapport avec la clinique*, XXII Cong. de la Soc. italienne de med. int., Rome, oct., 1912.

<sup>4</sup> G. Ghedini, *idem*.

<sup>5</sup> Parhon, *Les gl. à secrét. int. dans leurs rapp. avec la psychol. et la pathol. mentale*, rapport, Congrès internat. de Neurol., Gaud, 1913.—Voire aussi: Parhon et Goldstein, *Les secrét. int.*, Maloine, 1909; W. Falta, *die Erkrankungen der Blutdrüsen*, Berlin, 1913; Lucien et Parisot, *Gl. surr. et org. chromaffines*, Gittler, 1913; Lewandowsky, *Handbuch der Neurologie*, Bd. IV, *Innere Sekretion und Nervensystem*, Berlin, 1913. See more complete Bibliography in Jelliffe and White, *Diseases of the Nervous System*, I, *Endocrinology*, 2d Edit., 1917.

psychic troubles caused by disorders of the glands of internal secretion, where I insisted on the importance of these glands in neurology and psychiatry, the glands of internal secretion, heretofore ignored, have now become the special study of medical men, so that all or nearly all of them, clinicians, anatomico-pathologists, experimenters and therapists started investigating and consequently to-day one invokes with too much facility their disturbances as a causative factor each time one is puzzled. Next to the sympathetic, the abnormalities of which were more dwelt upon than was warranted, the endocrine glands have become the maids of all work of physiopathology.

It seems wise to me to expostulate against this excess. It has a tendency in effect to prejudice against endocrinology such critical minds which are more impressed by the lack of strict truth and the foundation of vagrant theories than by the biological interest of precise facts, verified over and over again.

In this question of the relationship of the internal secretions and the nervous system one should be assured above all of the reality of the facts under consideration, then these should be analyzed as to their details in order to grasp their divers elements, and to unravel their component parts, finally one should not extend their reach beyond the conditions that determine them, extrapolation not being generalization.

From the standpoint of pathology as from the standpoint of physiology the relations of the internal secretions and the nervous system interest us in so much as they are relations of causality.

My first aim then is to show that in pathology there exist, on the one hand, nervous disorders due to disturbance of the internal secretions, and on the other hand, disturbance of the internal secretions due to nervous disorders.

Before establishing this double relationship it is necessary to define exactly the terminology. Nervous troubles mean to me all the disturbances of the nervous system, the motor symptoms, sensory symptoms, trophic and psychic symptoms with their anatomical, physical and chemical correlations. These disorders are divided into three groups according as to whether they pertain to the sensory-motor, vegetative or psychic functions.

The sensory-motor disturbances are above all the expression of the neuraxis, the vegetative of the vago-sympathetic, and the psychic of the cerebral cortex.

One knows that Langley has differentiated in the vegetative

system that which he calls the autonomic from the sympathetic system. This consists of the cephalic portion which proceeds from the mid-brain and the bulb—the oculomotor nerve, the pneumogastric and the chorda tympani—and of the sacral portion running from the cord—the pelvic nerves. This system, of which the ruling element is the pneumogastric, presents a functional antagonism to the sympathetic.

Thus, for example, the sympathetic dilates the pupil, causes the eyeball to protrude, accelerates the heart action, inhibits the movements of the intestine, dilates the sphincter ani, produces glycosuria and polyuria. Inversely the autonomic system contracts the pupil, relaxes the zonule of Zinn, slows the heart action, contracts the muscles of the intestine, increases the gastric and pancreatic secretions.

Eppinger and Hess<sup>6</sup> have striven to demonstrate this in man by the aid of pharmacodynamic tests, injections of adrenalin, of pilocarpine and of atropine. They have given the name of vagotonics to individuals in whom the activities of the autonomic predominate and of sympathicotonics to individuals in whom the sympathetic excels.

Adrenalin dilates the pupil, contracts the blood vessels, accelerates the heart action, increases arterial tension, produces polyuria, glycosuria and reflex excitability.

Pilocarpine incites salivation, sweating, blushing, increase of intestinal peristalsis, hypersecretion of digestive fluids and intestinal juice.

Atropine dilates the pupil, stops secretion, and sometimes accelerates the heart.

Eserine, introduced by Mougeot,<sup>7</sup> vago-excitant, slows the pulse, raises pressure, and contracts the intestine.

One speaks of adrenalin as exciting the sympathetic, of pilocarpine and eserine as exciting the autonomic, and of atropine as paralyzing the latter.

When a subcutaneous injection of one milligram of adrenalin produces a glycosuria in excess of 5 grams, when the quantity of urine is doubled and the pulse has a rhythm one third above normal, one speaks of sympathicotonia.

<sup>6</sup> H. Eppinger et L. Hess, *Zur Pathologie des vegetativen Nervensystems*, Deutsch. Arch. f. klin. Med., 1909, LXVIII, 3-4, p. 231. See Monograph No. 20, this series. Translated by Kraus and Jelliffe.

<sup>7</sup> Mougeot, A., *Le réflexe oculo-cardiaque*, Soc. de Med. de Paris, 28 mars, 1914, pp. 277-287.

When a subcutaneous injection of one centigram of nitrate of pilocarpine produces a salivation and sweating more abundant than normal one speaks of vagotonia.

When a subcutaneous injection of one milligram of the neutral sulphate of atropine produces a rapid and prolonged dilatation of the pupil with considerable increase of the pulse rate one speaks again of vagotonia.

When finally a subcutaneous injection of a quarter of a milligram of hydrobromate of eserine does not produce an appreciable slowing of the heart nor contractions of the intestines one speaks either of hypovagotonia or sympathicotonia.

The oculo-cardiac reflex, discovered by Aschner, allows one also to take notice of the respective activities of the sympathetic and pneumogastric

In the normal state and in the recumbent position, pressure on the eyeballs with the pulp of the fingers softly for 30 seconds without pain, determines after the lapse of a few seconds a slowing of the pulse, lowering of arterial tension, slowing of the respiration and sometimes a feeling of nausea.

The reflex is positive when the slowing of the pulse is in excess of 12 beats per minute.

It is normal when the slowing is at least 4 and less than 12 beats per minute.

It is negative when there is no reaction or one of less than 4 beats per minute.

It is inverted when, without excitement or pain, the slowing of the pulse is replaced by acceleration.

When the reflex is positive, one speaks of vagotonia; when it is negative or inverted, of sympathicotonia.

Thus, thanks to these researches, two clinical types among the vegetative neurotics are clearly determined.



## CHAPTER I

The young girl, who complains of palpitations and precordial pains with slight tachycardia, burning pains in the stomach, diarrheas and sweating attacks, in spite of being chilly and having cold feet; who has profuse lachrymation, who is often nauseated, and who has tendencies to be sick especially before her periods, who is easily seasick, who dislikes to ride backwards in a carriage or railroad car; who with a large palpebral fissure has a slight exophthalmos; who has a clear von Graefe's sign without the sign of Möbius; who has an abnormally low arterial tension, with perhaps an eosinophilia; whose overcontracted pupils are not dilated by adrenalin, and which contract with expiration (Samogyi's sign); who has an alimentary glycosuria with adrenalin; who has secretory crises with pilocarpine; and finally who is benefited marvellously by atropine as regards dyspeptic troubles, and whose constipation disappears at once—she is a vagotonic.

The woman with a well-marked tachycardia and few subjective symptoms; with exophthalmos and no von Graefe's sign, but with a clear sign of Möbius; with a large pupil and scanty lachrymal secretion; who has no sweats or diarrheas; with very marked loss of hair, with a tendency towards fever; who is always too warm; whose pupil dilates with adrenalin, who also has an alimentary adrenalin glycosuria; who does not react to pilocarpine, and stands atropine badly—she is a sympathicotonic.

This differentiation, true in general, has aroused many criticisms from the very first, especially from Fleischmann,<sup>8</sup> Potzl, Eppinger and Hess themselves,<sup>9</sup> Falta, Newburgh and Nobel,<sup>10</sup> Falta and Kahn,<sup>11</sup> Petren and Thorling,<sup>12</sup> Burstein<sup>13</sup> and Bauer,<sup>14</sup> etc., the justice of which has been admitted by myself and my interne Mlle. Romme at Beaujon Hospital.

It is thus that we have seen intense reactions to pilocarpine at the same time that adrenalin shows an exaggerated excitability of

<sup>8</sup> Fleischmann, *Med. Klinik*, 4 fev., 1910.

<sup>9</sup> O. Pötzl, H. Eppinger et L. Hess, *Wien. klin. Woch.*, 22 dec., 1910.

<sup>10</sup> W. Falta, L.-H. Newburgh et E. Nobel, *Zeitschr. f. klin. Med.*, 1914, LXXII, 1-2.

<sup>11</sup> W. Falta et F. Kahn, *Zeitschr. f. klin. Med.*, 1912, LXXIV.

<sup>12</sup> K. Petren et I. Thorling, *Zeitschr. f. klin. Med.*, 1912, LXXIII, 1-2.

<sup>13</sup> M. Burstein, *Med. Obozr.*, 1912, LXXII, 10.

<sup>14</sup> J. Bauer, *Deutsch. Arch. f. klin. Med.*, 1912, CVII, 1.

the vegetative system, the same individual presenting at intervals of some days different reactions, and adrenalin glycosuria has no value until the hepatic element is eliminated.

Finally I wish to state that the term tonic or tone does not seem to me well chosen, because it deals more with an exaggeration of the excitability of the nerve rather than an increase of its tonicity, and these two states are far from being always parallel.

Be that as it may, I differentiate in nervous disorders in addition to sensory-motor troubles and psychoses, the disorders of the vegetative system, and these sympathetic and autonomic abnormalities. We shall see later on that these disorders do not separate themselves into parallel series as simply as the theory would have them do. Then again many trophic disorders observed in endocrine syndromes are not actually trophoneuroses. It seems quite often that endocrine commotions reach on the morphology through a humoral intermediary and not through a nervous one. Nevertheless, as I can not dissociate in the actual enumeration of the trophic disorders those that have a nervous intermediary from those that have none, I will discuss them all, later on indicating how they may be distinguished.

Commutations of the internal secretions should include the disturbances of all the internal secretions, that is to say, all humoral pathology not to say all the pathology, because every cell from a cytological standpoint is a gland of internal secretion, and following Renault, who showed the secretory value of the cells of the conjunctivæ, Nageotte, just recently by mitochondrial methods, has demonstrated the secretion of the neuroglia, which was thought formerly to be a simple tissue of support.<sup>14a</sup>

In order to be brief, and admitting the three distinctive conditions, histological, chemical and physiological, of the glands of internal secretion, claimed by Gley<sup>15</sup> at the recent Congress of London, I will only picture among the internal secretions those that depend upon definite glands, in the front ranks of which I will place the classical hemato-vascular glands: thyroid, parathyroids, pituitary, suprarenals, ovaries and testicles.

I will add to this group the pineal, which in the infant, histologically as well as physiologically, is an endocrine gland; the choroid plexus, of which the secretion diffused in the cerebro-spinal fluid has been demonstrated by Pettit and Girard; the prostate, whose

<sup>14a</sup> See Translation of Achucarro, *Jl. Nervous and Mental Disease*, Oct., 1918, p. 333.

<sup>15</sup> E. Gley, *Relat. entre les organes à sécrétion int. et les troubles de ces secrét.*, Rapport, sect. de Physiol., Congrès internat., Londres, 1913.

elective action on the genital organs has been brought in evidence by Hallion, Papin and Morel<sup>16</sup> and the paraganglia of the sympathetic, which are chromaffin organs apart from the suprarenals.

In addition among the glands of external secretion, certain ones have at the same time an internal secretion of such importance that I must at least mention them; such are the liver, the kidney, the pancreas, the salivary glands, the mammary glands and the intestinal glands of which the endocrine action has been grasped histologically by P. Masson.<sup>17</sup> Among these I will retain only the pancreas on account of its participation in the mechanism of glycosurias.

Finally among the lymphoid glands, ganglia, thymus and spleen, the thymus at least plays a secretory rôle.

I will consider then the nervous disorders linked with disturbances of the thyroid and parathyroids, the thymus, the suprarenals and paraganglia of the sympathetic, the pancreas, the pituitary, the pineal and the choroid plexus, the ovary, the testicles and the prostate.

In this clinical analysis I shall recapitulate at first in a critical review as briefly as possible the nervous disorders existing in the syndromes, that one as a rule places among the disturbances of the endocrine glands, that I have just mentioned, and reciprocally the endocrine disorders observed in the nervous syndromes.

In this critical review I will bring out the elements of an endocrino-neurological scheme, in which by the choice of certain nervous symptoms, certain endocrino-vegetative syndromes, certain traditional nervous syndromes, certain temperaments, certain characters, I will attempt to show by the method of double weighing, that some among them are determined by an endocrine commotion in certain cases, and that in others they are the expression of a nervous upheaval of different origin reacting secondarily on the internal secretions.

And I will gather from this rather suggestive study of a subject so complex and so obscure some conclusions which I will advance for your discussion.

<sup>16</sup> Hallion, Morel et Papin, *Act. vaso-dilatatrice péniesme de l'extr. prostateq.*, Soc. de biol., 28 fev., 1913, p. 401.

<sup>17</sup> Masson, P., *La gl. endocrine de l'intestin chez l'homme*, Acad. des Sc., 5 janv., 1914.

## A. CRITICAL REVIEW

The endocrino-neurological clinical relationships form, a priori, two big groups:

1. Nervous disorders in the endocrine syndromes.
2. Endocrine disorders in the nervous syndromes.

Before discussing these I must explain the value of the methods of investigation which are permissible for proof. I will be very brief as regards the neurological methods and a little more explicit as regards the endocrinological procedures.

*(a) Methods of Neurological Investigation*

I skim over the current clinical methods employed for unraveling the motor, sensory, lisso-motor, secretory, trophic and psychic disorders of the nervous system to pause at the more complex experimental tests in clinical use to establish the so-called states of vago- and sympathicotonia. These tests are at the starting point chemical or mechanical. The first are the injections of adrenalin, of atropine, of pilocarpine, of eserine; the second are the ocular, auricular or solar ganglion tests permitting the consideration of the oculo-cardiac,<sup>18</sup> auriculo-cardiac and coeliac hypotensory reflexes.<sup>19</sup>

Now each of these tests determines a series of reactions already quoted.

In order to judge of their diagnostic bearing on the neurological status one makes three hypotheses.

The first, that the antagonism between the sympathetic and the autonomic is complete.

The second, that just one of the results of each of the tests, which one regards as characteristic, is representative of the general orientation of all the results of that test.

The third, that the orientation of the test so determined is of use for deciding not only the state of the function thus investigated, but the state of the whole sympathetic or autonomic nervous system.

Now as regards the first hypothesis one can reply that if pharmacodynamics bring the innervation of the sweat glands under the control of the autonomic, there is nothing in anatomy or physiology to permit it to be separated from the sympathetic.

To the second one can answer that the results so often dis-

<sup>18</sup> For the recent French bibliography, see: Vernet et Petzetakis, *Le réflexe oculo-cardiaque*, *Gaz. des hôp.*, 2 mai, 1914.

<sup>19</sup> André, Thomas, et J., *Ch. Roux. Soc. de biol.*, 23 mai, 1914, p. 857.

sociated of adrenalin or atropine, raised blood pressure without glycosuria or vice versa, dilatation of the pupil without acceleration of the heart or vice versa, show clearly that one can not draw conclusions from the character of the physiological reaction, considering from the same standpoint the character of all the other possible reactions that one has neglected.

In a stronger way one should respond to the third hypothesis that the frequent confirmation of reactions in an inverse sense, of the vagotonic and sympathicotonic classification shows that one can not judge of such states from one single reaction, but further that the frequent confirmation of reactions in an inverse sense, sympathicotonic or vagotonic, that I have often observed as a result of different tests and even of the same test, shows at least the association or the succession of these two states of the vegetative system, and in consequence diminishes, if not the importance of the doctrine, at least the practical interest of this classification, of which the clear-cut outlines and the antagonism seem to have been exaggerated.

### *(b) Methods of Endocrinological Investigation*

These methods are clinical, anatomical, organotherapeutic, physiological and chemical. In my report of 1908 I have shown the inherent causes of error in the first three.

Clinically one must not in an endocrino-neurological complex, of which the groupings may be more or less defaced, pick out as an element of causality that which perhaps is nothing more than a co-result of the same cause or which has nothing but a contingent relationship with the nervous or endocrine disorder.

In anatomo-morphological pathology one gathers facts of incontestable value, and that is why I have continued<sup>20</sup> to examine systematically the endocrine glands of my nervous and mental cases, but as I said in 1908 one must always know how to read, and how to interpret these data; to read them, that is to say, ob-

<sup>20</sup> Laignel-Lavastine, Hyperplasies glandulaires de l'hypophyse. Congrès de Neurol., Amiens, 1911.

Laignel-Lavastine et Duehm, Les parathyroïdes chez les aliénés, Soc. de biol., 20 janv., 1912; 30 mars, 1912; Annales de Méd. (sous presse); Les parathyroïdes chez les déments séniles, Soc. de psychiatrie, avril, 1912; M. Labbé, Laignel-Lavastine et Vitry, Diabète et lésions du pancréas, Soc. anatomique, 8 mars, 1912.

Laignel-Lavastine et V. Jonnesco, L'hypophyse des psychopathes, Soc. anatomique, 30 nov., 1912; Encéphale, janv., 1913, pp. 25-45. Trois planches couleurs.

Laignel-Lavastine, Anat. pathol. de la pinéale, Mém. couronné par l'Acad. de Méd., 1913, Arch. de Méd. exp. (sous presse).

serve the physiological, ethnic or geographical<sup>21</sup> variations, the errors of technique, the post-mortem lesions, in order to distinguish the normal from the pathological; to interpret, that is to say, to distinguish in the pathological lesions those which are contingent, and are recent alterations due to terminal accidents, or which are but a co-effect resulting from the same cause as the nervous disorders, or results of a previous infection or intoxication, in order to be able with these lesions to establish beyond criticism a causal relationship between endocrine disorders and nervous symptoms.

Besides a last difficulty which is considerable renders these researches sufficiently rare under ideal conditions. The glandular disorders, which for the sake of argument one supposes to have reacted on the mental condition, are seldom severe enough to result in death.

A long time elapses between the onset of the trouble and the autopsy. Thus on the one hand additional lesions due to the pathological overcharge can render old glandular lesions unrecognizable, and on the other hand nervous and psychic symptoms born of a glandular disorder, which is often transitory, may outlast this disorder indefinitely.

These examples of nervous and above all mental sequelæ of a functional upset, which has ceased for a long time, are relatively very frequent illustrations of the great law of habit.

In organotherapy<sup>22</sup> when it is a question of establishing a relationship of causality between a nervous disturbance and an endocrine disorder, because the administration of the extract of an incriminated gland has been followed by the disappearance or at least the attenuation of the nervous syndrome under consideration, it behooves one to be even more careful than in any other therapeutic induction, being aware already of the many fallacies of such because here the causes of error are particularly numerous: coincidence; general action on the organism and its metabolism by simple pharmaco-dynamic effect; suggestion; variability of the organotherapeutic extracts according to the method of acquisition, of preparation, of conservation, their age, the mutation of effect according to dosage, the avenue of introduction, the frequency of dosage, the difference between their action and that of the normal

<sup>21</sup> Il en est aussi pour la thyroïde. V. Parhon, Mlle. Mateesco, Tupa, *Nouv. recherches sur la thy. des aliénés, Encéph.*, août-sept., 1913, pp. 139 et 235-55.

<sup>22</sup> Hallion, L., *La pratique de l'opothérapie*, 1911.

gland, the uncertainty indeed of the nervous syndrome being in line with the endocrine disorder, which in other respects may not have induced the nervous syndrome except through the agency of glandular commotions in one or many other of the endocrines, observing as well other intermediaries such as mechanical, physical, chemical, humoral, nervous or psychic causes.

In his report of 1913, Gley reiterated the causes of error in insisting upon the general toxicity of organic extracts and their variations, depending upon the method of preparation, autolysis, the production, the manner in which they are used, the heating and the quickness of injection. In addition he has drawn attention to a new cause of error: tachyphylaxis,<sup>23</sup> rapid immunization characterized by the fact that successive injections of organic extracts in small doses gives rise to an immunization that is produced in a few minutes. This phenomenon of tachyphylaxis for one organic extract can be aroused by the extract of another organ and vice versa. This crossed tachyphylaxis of Gley and Champy should be taken into consideration in the interpretation of such complex results as the effects of treatments by simultaneous or successive associations of glandular extracts. From this standpoint the theory of treatment by hormones<sup>24</sup> is guarded from such causes of error because the hormones entail neither anaphylaxis nor tolerance. In the above we have an instance of one of the differences between the action of adrenalin and that of extracts of the suprarenal gland.

Finally the new physiological methods, methods of Abderhalden, methods followed by Gley and Claude, etc., are themselves no longer shielded from causes of error.

The Abderhalden method has already been applied by numerous authors, Urechia,<sup>25</sup> Pesker,<sup>26</sup> Parhon,<sup>27</sup> Obregia and Pilulesco,<sup>28</sup> Marinesco and Papazolu,<sup>29</sup> Mutermilch,<sup>30</sup> etc., to induce from their results an endocrinological origin for numerous nervous and mental syndromes.

Only recently, following his researches on the relations of the

<sup>23</sup> Gley et Champy, Soc. de biologie, 1911, 22 juillet, p. 159; Gley, Livre jubilaire du Pr. Richet, 1912, pp. 111-29.

<sup>24</sup> Hallion, L., Sur la part attribuable aux hormones dans les effets de l'opothérapie, Soc. de thérapeutique, 26 nov., 1913, pp. 472-77.

<sup>25</sup> Urechia et Popeia, Soc. de biol., Bucarest, 20 dec., 1913, p. 591.

<sup>26</sup> Pesker, Ass. scientif. des med. de l'Ass. psychiatrique Saint Nicholas a Saint Petersbourg, 10 janv., 1914.

<sup>27</sup> Parhon, et Parhon, M., Soc. de biol., 25 avril, 1914.

<sup>28</sup> Obregia et Pitulesco, Soc. de biol., Bucarest, 31 janv., 1914, p. 316.

<sup>29</sup> Marinesco et Papazolu, Soc. de biol., Bucarest, 29 mai, 1914, p. 1419.

<sup>30</sup> Mutermilch, S., L'applicat. de la réact. d'Abderhalden au diagnostic et à l'état des mal. nerv. et mentales, Arch. de Neurol., avril, 1914, pp. 205-219. Bibliographie.

internal secretions and the psychoses, Parhon, with Odobesco,<sup>31</sup> started to trace a psycho-endocrine syndrome characterized from the psychic viewpoint by great irascibility and ideas of persecution poorly systematized, and from a somatic viewpoint by ovarian disturbances, irregular menstruation or amenorrhea and especially thyroidal disturbances, congestion of the face, hot flashes, mononucleosis and a positive Abderhalden reaction for the thyroid.

Now Plaut has shown that in Abderhalden's reaction, kaolin talc, sulphate of barium produce dialyzable substances which react with ninhydrin just as the protein does which has served in the preparation of the animal,<sup>32</sup> and H. de Waele concluded after a series of experiments that this ferment is unique: it is antithrombin. It is not the fragments of organs or proteins that undergo proteolysis but really the globulins of the serum. The specificity will simply arise from the preparatory injection which has created conditions favorable to the action of the protein on the globulins of the serum, and it appears probable that this bears a close relationship to the phenomena of agglutination and precipitation.

Even more recently Flatow<sup>33</sup> happened to show that it consists of simple variations of the proteolytic ferments of the serum. This study of antiferments for the diagnosis of endocrino-nervous relationships is, therefore, to my mind, extremely dangerous. In effect the recent criticisms of the Abderhalden reaction, in spite of the recognition of the gross chemical interest, put one justly on guard against its pretended specificity towards the extracts of organs employed.

I will then consider that the new investigations are not entirely conclusive relative to the existence of an endocrine factor, based solely on the Abderhalden reaction.

The physiological method advocated by Gley in his report for judging of the functional capacity of the affected organ consists of injecting into animals the altered tissue in order to see if it still manifests the physiological properties of normal tissue.

A priori, this method seems of value, and, as Gley says, "this type of study seems to recommend itself in a general way to pathologists. The anatomo-pathological research which allows certain lesions to be authenticated should be amplified." And as an

<sup>31</sup> C. J. Parhon et Gr. Odobesco, *Encéphale*, 10 juin, 1914, pp. 489-582.

<sup>32</sup> H. de Waele, *Soc. de biol.*, 25 avril, 1914, p. 627, et *Zeitschr. f. Immunitätsf.*

<sup>33</sup> Flatow, A propos de la spécificité des soi-disant ferments protecteurs, XXXI Cong., allemand de med. int., Wiesbaden, mai, 1914.



example he has cited his experiences with the cardio-vascular action of adrenal extract from thyroidectomized dogs compared with that obtained from normal canine glands. He did not note any difference. Porak, who has followed this route, has arrived at unexpected results. Suprarenal extracts obtained under conditions of activity clearly greater than normal have given cardio-vascular reactions of less intensity than those that were obtained under normal conditions. As the cardio-vascular effect is proportionate to the richness in adrenalin one must conclude that not only is the richness in adrenalin of the suprarenals not in proportion to their activity, but that taken at a given moment they are less charged with adrenalin than are less active suprarenal glands.

Thus because function wears itself out with persistence, and by fault of having overlooked the time factor, one has been exposed to erroneous deductions, in conclusions drawn from the physiological method, which a priori is valuable in itself.

It is good because, contrary to precedent, it is capable of furnishing answers during the life of the individual. Better yet because it seems to be the method followed by Claude and his pupils.

It consists of injecting divers glandular extracts into patients, and observing their reactions systematically, and deducing from these reactions the probable endocrine disorders. Thus it permits the acquisition of individual indicators of physiological endocrine reactions, which, counting on the complexity of the cases, by the comparison of a large number of facts, may allow the formation of hypotheses if not of conclusions. Claude with his pupils, Baudouin and Porak, has already used this method with success in the study of acromegalics, Addisonians and just recently of Basedowians.<sup>34</sup>

The many criticisms summed up by Biedl and Falta and Porak<sup>35</sup> have done full justice to the serological methods, such as that of Meltzer-Ehrmann, based upon the supposed fact that dilatation of the enucleated eye of the frog, in the presence of any serum indicates the existence of adrenalin in that serum. Mydriasis can be brought about by other causes than the presence of adrenalin. It is useless to argue further.

There remains the need of knowing how to interpret the results of the clinical, organotherapeutic, anatomo-pathological and physiological methods (Claude type).

<sup>34</sup> Claude, H. Baudouin, R. Porak, L'épreuve des extr. hypophysaires chez les basedowiens, Soc. méd. des hôp., 19 juin, 1914, 1112.

<sup>35</sup> Porak, L'épreuve de l'hypophyse dans les maladies des glandes à sécrétion interne., Thèse, 1914.

I will now sum up the nervous disturbances in the endocrine syndromes and the endocrine disturbances in the nervous syndromes as rapidly as possible, because one finds them to-day explained at length everywhere.

### 1. Nervous Disturbances in the Endocrine Syndromes

Endocrine syndromes are increasing every day, perhaps because one finds definite endocrinal lesions in a syndrome till now confounded with an analogue, perhaps because one now erects at pleasure endocrine theories for divers affections of unknown origin. The first way is legitimate, although of a rather delicate interpretation—in fact we are all familiar with the frequency of lesions in the endocrine glands in all sorts of autopsies. The second is singularly fallacious when it depends only on experimental or clinical analogies or on debatable anatomical, humoral or therapeutic authentications. The syndrome of dystrophia adiposo-genitalis due to a pituitary lesion and precocious macrogenito-somatosis due to a pineal lesion are examples of the first. The endocrine theories as to the origin of seasickness, hysteria, Paget's disease, cholera are, in their turn, examples of the second.

In the beginning, in the period which might be called the uni-endocrine, each syndrome was connected with a lesion of one single gland, Basedow's with the thyroid, Addison's with the suprarenals, acromegaly with the pituitary, and in each gland only disorders of increase or decrease of secretion were seen (quantitative period).

In the meantime, after many others, I had shown with Thaon in 1905 a case of Basedow's disease in a woman with myxedema, which the simple quantitative theory could not explain.

Meanwhile, in 1904, in reference to a case of acromegaly with hypertrophy of the pituitary, the thyroid and the suprarenals, I and M. Ballet<sup>36</sup> attempted to explain these glandular reactions by claiming functional correlations among the endocrines, and I advanced the hypothesis of a humoral process.

Shortly after, Claude<sup>37</sup> insisted upon the existence of several endocrine reactions in acromegalics.

After this quantitative, uniendocrine organic period there followed the polyendocrine period, which is rendered memorable by the ringing memoir of Claude and Gougerot<sup>38</sup> on the pluriglandular

<sup>36</sup> G. Ballet et Laignel-Lavastine, Soc. de Neurol., juillet, 1904, R. N., p. 793.

<sup>37</sup> Claude, Soc. de biol., 28 oct., 1905, p. 362.

<sup>38</sup> Claude et Gougerot, Soc. de biol., dec., 1907, p. 785. Journ. de physiol. et path. gén., juin, 1908.

syndromes pertaining to a tuberculous case with a testicular-adrenothyroidal insufficiency.

Subsequently on June 24 at my course at Laennec on the medical anatomy and physiology of the secretions I delivered a lecture, published afterwards,<sup>39</sup> on the correlation of the glands of internal secretion and their pluriglandular syndromes, and M. Renon<sup>40</sup> established a clinic at Necker.

Following this one spoke of nothing but pluriglandular syndromes, because really the disorders are hardly ever, if ever, limited to one gland exclusively. But after having been too limited, we exaggerated in the opposite sense. It is not logical, because the endocrinal disorders in the pathological state have many glandular echoes, as in the normal state the functional correlations run along in humoral harmony, to speak of pluriglandular syndromes when but two glands are involved.

In addition if classical endocrine syndromes such as Basedow's syndrome, Addison's syndrome and diabetes insipidus are often allied to a microscopical lesion of the thyroid, the suprarenals or the pancreas, sometimes these lesions lack emphasis, and one is forced to admit a nervous disorder reacting on these glands. It is this that I endeavored to demonstrate in my theses on the solar plexus,<sup>41</sup> where side by side in Addisonian syndromes with microscopic lesions of the suprarenals I published others without such lesions. As I have stated, a syndrome being the clinical expression of a disturbance of function, it is brought about either by a glandular lesion which controls that function or by a lesion of the nervous system, which regulates that gland. To the lesional contingency is opposed the functional necessity. All the cases which are not explained by the organic theory place themselves easily, on the contrary, in the physiological theory, which is much more comprehensive. Hence one must know how to substitute the single physiological or the qualitative or quantitative polyendocrine explanation for the quantitative organic uniendocrine interpretation which is the oldest and simplest.

To sum up, endocrine syndromes may depend not only on a lesion of a corresponding gland or of its regulating nervous mechanism, but indeed upon an upset of one or the other of an infectious or toxic origin; the glandular trouble may be not only quantitative but qualitative; it may depend not only on one gland but upon

<sup>39</sup> Laignel-Lavastine, *Gaz. des Hop.*, 14 nov., 1908, pp. 1563-71.

<sup>40</sup> Renon, *Journ. des praticiens*, 25 juill., 1908.

<sup>41</sup> Laignel-Lavastine, *Thèse de Paris*, 1903.

many, and in the latter case with predominance on one or on several of them, sometimes without appreciable clinical ascendancy. I will therefore enumerate the uniendocrine syndromes and the polyendocrine syndromes, and I will divide the latter into two groups according as to whether a preponderance in the disorders of certain glands can be differentiated or not.

From this enumeration of the endocrine syndromes it will become evident that endocrinogenous nervous disorders exist. The interpretation of facts is more delicate from the viewpoint of the Viennese School, which, in a parallel manner to the division of the vegetative system into sympathetic and autonomic systems, and after having admitted the relationship of excitation and inhibition of the divers glands, one on the other (the triangular schema of Eppinger, Falta and Rudinger reproduced everywhere), divides these same endocrine glands into two groups, of which one formed especially of the suprarenals, the thyroid and the pituitary excites the sympathetic, while the other formed especially of the pancreas and parathyroids excites the autonomic.

#### A. UNIENDOCRINE SYNDROMES

The ensuing is the enumeration of nervous disorders noted in the divers syndromes as depending on the following endocrine glands: thyroid, parathyroids, thymus, suprarenals, paraganglia of the sympathetic, pancreas, pituitary, pineal, choroid plexus, ovary, testicle and prostate.

##### 1. *Thyroid*

1. *Myxedema*: Arrest of development, dwarfism, infantilism, infiltration of the skin, mental torpor, dull ideation, defective memory, apathy, laziness, sluggishness, somnolence, taciturnity, awkwardness, slow, monotonous, raucous, nasal voice; small pulse, rapid and irregular, sometimes with hypertension; constipation, scanty urine, subnormal temperature, chilliness, headaches, slight knee jerks; no alimentary glycosuria; sometimes epilepsy.

2. *Basedow's syndrome*: Tachycardia, arrhythmia, anxiety, pulsation of the arteries of the neck: exophthalmos, lachrymation. Von Graefe's sign (lack of synergy in the movements of the upper eyelid and the globe), Stellwag's sign (lengthening of the palpebral fissure and incomplete closure of the eyes), Möbius's sign (difficulty in convergence); facial paresis, a giving way of the legs, epilepsy, transient attacks of tetany, cramps, tremblings, ocular frontal headaches; colics, hot flushes, profuse sweats, intolerance of

heat, vasodilatation of the skin, meningitic skin reaction, dermographia,<sup>42</sup> transient attacks of edema, pigmentations, urticaria, alopecia, diminution of electrical resistance, polyuria, albuminuria, glycosuria, anorexia, insatiable hunger, vomiting, ptyalism, hyperchlorhydria, diarrhea, rapid respiration, Bryson's sign (lack of deep inspiratory power), suffocation, amenorrhea, atrophy of the breasts, emaciation, agitation, emotional instability, volubility, insomnia, emotional stress, susceptibility, inquietude, anxiety, rage and sometimes anxiety neurosis, obsessions, anxious melancholy, cyclic insanity, restless excitement, depression, mania, melancholia, mental confusion, epilepsy.

Sainton<sup>43</sup> found among Basedowians sometimes signs of sympathicotonia: exophthalmos, adrenalin mydriasis, lack of lachrymal secretion, violent tachycardia, glycosuria, adrenalin reaction, an absent or inverted oculo-cardiac reflex; at other times signs of vagotonia: slight exophthalmos with enlargement of the palpebral fissure, Von Graefe's sign, increased lachrymation, abundant sweats, diarrhea, slight tachycardia, no alimentary glycosuria, positive oculo-cardiac reflex and a pilocarpine reaction; and at still other times a mixture of the two series.

He therefore admits of three forms: sympathicotonic, vagotonic and mixed.<sup>44</sup>

This seems to me to be the rule. Especially as I have had occasion to see a case where the oculo-cardiac reflex was at various periods sometimes positive, sometimes normal, negative and even inverted.

3. *Thyroidal insufficiencies other than myxedema*: Infantilism, obesity, Dercum's syndrome, pseudo-lipomatosis, alopecia, premature grayness, scleroderma, urticaria, pruritus, relapsing herpes, transitory edemas, migraine, asthma, constipation, muco-membranous entero-colitis, blueness of the extremities, Raynaud's syndrome, localized erythema, nasal asthma, carbohydrate tolerance, genital irritability, hypertrophy of the mammæ, chilliness.

4. *Thyroidal instability of Leopold Levi and Henri de Rothschild*: (a) With dyshypothyroidea predominating: chilliness, falling of the hair, headaches, despairs, weeping fits, giddiness, transient edemas, pains, spells of suffocation, shivering fits, hot flushes at the periods; (b) With dyshyperthyroidea predominating:

<sup>42</sup> Alquier, Rev. Neurol., 30 mars et 30 juin, 1914, pp. 393-401 et 795.

<sup>43</sup> Sainton, P., Journ. méd. français, 15 mars, 1914.

<sup>44</sup> B. Guillaumont, Le réflexe oculo-cardiaque dans le syndrome de Basedow, Th., 1914, p. 74.

emaciation, heavy eyebrows, flashes of heat, feverishness, palpitation of the heart, intestinal spasms, irritability, emotivity, phobias, inquietude, overwhelming migraines, asthma, hyperidrosis, dysidrosis, tremblings; (c) Without preponderance: chilliness, chills, migraines, repeated trips to the toilet, migratory pains, "diffuses," "hemmage," redness of the eyebrows, catamenial neuralgias, anxieties, large palpebral fissure, swelling of the feet, variability in the size of the extremities, tremors, nervous crises, hysteria.

## 2. Parathyroids

1. *Tetany*.<sup>45</sup> Tingling and stiffness of the fingers, tonic intermittent spasms of the flexors of the extremities; flushings, temporary edemas of the joints, normal or increased tendinous reflexes, dyspnea, tachycardia, fever, salivation, vomitings, diarrhea, Trousseau sign (hand of the accoucheur on compression of the arm), Chvostek's sign (brisk and fleeting contraction of the skin muscles of the face on light percussion of the facial nerve, over the auriculo-labial course) and Weiss's sign (brisk contraction of the muscles of the forehead, eyebrows and eyelids on light percussion of the temporal branch of the facial at the level of the external angle of the eye); hyperexcitability of the nerves to the galvanic current, particularly to the closure of the negative current and the opening of the positive current.

2. *Parkinson's*<sup>46</sup> *syndrome*?: Trembling, muscular rigidity, propulsion, rheumatoid pains, sensations of heat, increased tendinous reflexes, vaso-dilatation, sweats, edemas, cerebral retardation, psychic depression, vertiges.

## 3. Thymus

1. *Vagotonic symptoms*<sup>47</sup> of *Basedow's syndrome* (?): Profuse sweats, palpitations, lymphocytosis, eosinophilia, sensation of weakness.

2. *Myasthenia*<sup>48</sup> of *Erb-Goldflam* (?): Headaches, ptosis, ex-

<sup>45</sup> Tetanie, résultante d'une insuffisance parathyroïdienne latente, congénitale or acquise, qui s'aggrave brusquement et devient manifeste à l'occasion d'une traumatisme, d'une infection or d'une intoxication surajoutée. Thèse de R. Lifschitz, 1914, inspirée par Babonneix.

<sup>46</sup> Le syndrome de Parkinson serait hypoparathyroïdien et s'opposerait à la myasthénie, syndrome hyperthyroïdien? (Lundborg). Deutsche Zeitsch. f. Nervenheilk., Bd. XXVII, 1904, p. 217; voir de plus: Gautier, J., Th., Lyon, 1913.

<sup>47</sup> Rose, Le thymus et la mal. de Basedow, Sem. med., 21 janv., 1914, d'après Capelle et Bayer, Biedl, Klose, Lampé et Liesegang.

<sup>48</sup> La coïncidence très fréquente d'une gros thymus chez les myasthéniques est certaine, Claude (Acad. de méd., juin, 1914) admet à l'origine de certains cas des lésions thymiques.

ternal ophthalmoplegia, changing and fleeting paralyses confined mostly to the head and neck, myasthenic electrical reaction of Jolly (muscular fatigue by tetanizing stimulation).

3. *Thymoprivic Idiocy* (Klose and Vogt).<sup>49</sup>

4. *Tetany??* (Basch).<sup>50</sup>

#### 4. *Suprarenals*

1. *Addison's syndrome and suprarenal insufficiency*: Asthenia, arterial hypotension, morning nausea, morning vomitings, lumbar pains, melanoderma, white skin reaction of Sargent, amyotrophia,<sup>51</sup> aboulia, sadness, sometimes: tetany, epilepsy, myoclonia<sup>52</sup> convulsions, periodic paralyses, delirium, mental confusion, coma, sudden death.

2. *Genito-suprarenal syndrome*: Feminine external pseudo-hermaphroditism with virile secondary sexual characteristics; suprarenal masculinism: amenorrhea, gynecomastia (excessive size of the male mammary glands), adiposity with discolorations of the skin, all signs of feminine maturity; in addition: hypertrophy of the clitoris, hypertrichosis with masculine distribution, masculine voice, increased muscular and nervous tonicity, violent character, "disorders of the mental state and affectivity may go as far as sexual inversion"<sup>53</sup> (Gallais); increased arterial tension, arteriosclerosis; glycosuria. "At the same time," adds Gallais,<sup>54</sup> "bizarre nervous and mental phenomena set in, near neighbors to maniacal excitement. The sexual instinct deviates: the character changes and becomes violent, authoritative, and crises of anxiety appear. Along with these crises and in the interim one notes vaso-motor phenomena."

#### 5. *Paraganglia of the Sympathetic*

Chromaffin cells in the solar plexus, Zuckerkandl's aortic paraganglia, the cardiac paraganglion of Wiesel and Wiesner, Luschka's carotid gland, Luschka's coccygeal gland, the tympanic paragan-

<sup>49</sup> Klose, H., et Vogt, H., *Klinik und Biologie der Thymusdrüse mit besonderer Berücksichtigung ihrer Beziehungen zu Knochen- und Nervensystem*, Beiträge klin. Chir., 69, p. 1, et Monographie, Tübingen, 1910 (505).

<sup>50</sup> Basch, K., *Über die Beziehung der Thymus zum Nervensystem*, Jahrbücher für Kinderheilkunde, 68, 1908.

<sup>51</sup> Sézary, *Syndromes surreno-musculaires*, Sem. méd., 5 fév., 1913.

<sup>52</sup> Laignel-Lavastine, *Les formes cérébrales de l'insuffisance surrénale*, Presse méd. d'Égypte, 15 mars, 1911, p. 89.—Frette, Th., 1913.

<sup>53</sup> A. Gallais, *Le syndrome génito-surrénal*. Thèse, Paris, 1913.

<sup>54</sup> A. Gallais, *Diagnostic anatomo-clinique du syndrome génito-surrénal*, Revue de gynécologie, janv., 1914.—Voir aussi: Truffier, *Virilisme surrénal*, Ac. de med., 27 mai, 1914.

gion, are for the most part<sup>55</sup> chromaffin organs, and in this respect pertain to the suprarenal sympathetic system. Their disturbances, from the standpoint of nervous echoes, have not, as far as I know at the present time, recognized aspects which are peculiar to themselves.

### 6. *Pancreas*

Diabetes mellitus: glycosuria, polyuria, polyphagia, polydipsia, neuralgias, pruritus, impotence, constipation, scant salivation, scant perspiration, dry skin, testicular atrophy, amenorrhea, loss of tendon reflexes, increased arterial tension, asthenia, headaches, lessened resistance to cold, perforating ulcer, syncopes, attacks of apoplectic form coma, paralyses, vertigoes, asthmatic dyspnea, pseudo-angina pectoris, somnolent disorders of sleep, depression, apathy, hypochondria, coma.

### 7. *Pituitary*

1. *Froelich's dystrophia adiposo-genitalis syndrome*: Adiposity, arrest of development or retrogression of the genital glands, genital organs and the secondary sexual characteristics corresponding thereto; somnolence.

2. *Renon and Delille's*<sup>56</sup> *syndrome of pituitary insufficiency*: Tachycardia, instability of the pulse, lessened arterial tension, insomnia, anorexia, painful sensations of heat, increase in the secretion of perspiration.

3. *Acromegaly*: "Marked hypertrophy, not congenital, of the upper and lower extremities and of the head," pain in the head, amenorrhea, tendinous reflexes never exaggerated, arrhythmia, syncope, sweats, polyuria, glycosuria, lessened resistance to cold, neuralgias, acroparesthesias, cramps, lancinating pains, lassitude, irritability, sadness.

4. *Giantism*: "Acromegaly in individuals in whom the epiphyseal cartilages are not yet ossified," impotence, amenorrhea, effeminacy, puerility, aboulia, asthenia, glycosuria, polyuria.

5. *Diabetes insipidus* (???)<sup>57</sup> Polyuria, polydipsia.

<sup>55</sup> Voir sur ce point les réserves de N. Pende, *Patologia de l'apparechio surrenale*, Milan, 1909; de C. Frugoni. La gl. carotidienne possède-t-elle une sécrét. int. propre? *Sem. méd.*, 9 oct., 1912, p. 481; de Lanzillotta, *Archiv. de Fisiologia*, 1 sept., 1913; et de Laignel-Lavastine, *Pathologie du sympathique* (sous presse).

<sup>56</sup> Renon et Delille, *Congr. de méd.*, act., 1907, et Delille Thèse, 1909.

<sup>57</sup> Il tiendrait à un trouble du lobe intermédiaire de l'hypophyse et de l'infundibulum. Harvey Cushing, *The Pituitary Body and Its Disorders*, Lippincott Co., Philadelphia et Londres, 1912; mais Camus et Roussy, *Soc. de biol.*, 1914, passim, l'ont reproduit expérimentalement par lésions de la substance grise du tuber cinereum au voisinage de l'infundibulum. Il desire chez le chien tout rôle à l'hypophyse dans la détermination du diabète insidiepe, *Presse méd.*, 8 juill., 1914, pp. 517-521.



### 8. Pineal<sup>58</sup>

1. *Macrogenitosomatosi*s:<sup>59</sup> Abnormal increase in growth or size, premature genital and sexual development with secondary sexual characteristics, hypertrichosis, precocious exaggerated mentality.

2. *Pineal adiposity*:<sup>60</sup> Diffuse obesity.

### 9. Choroidal Plexus

1. *Hydrocephalus*: Increased tension of the cerebro-spinal fluid, rapid reproduction, nervous and mental syndrome of ventricular hypertension, clouded mentality, idiocy.

### 10. Ovaries

1. *Infantilism*: Amenorrhea, absence of secondary feminine sexual characteristics, obesity, scanty hair, puerility.

2. *Acquired ovarian insufficiency*: Peripheral vaso-dilatation, crises of subjective sensations of heat, sweats, continuous or paroxysmal tachycardia, palpitations, increased arterial tension, insomnia, headaches, facial neuralgias, lumbago, neuro-muscular asthenia, uncertain memory, irritability, nervous debility, hysterical crises, exaggeration of the sexual instinct?, which is more often absent or inverted; obesity, inquietude, anxiety, phobias, impulses, gastro-spasm, constipation, vomiting, vertiges, syncopes.

"Vagotonic crises," before the periods and at the beginning of pregnancy: pallor, tendency to syncope, spells of nausea, vomiting, constipation, lessened arterial tension, rather slow pulse, positive oculo-cardiac reflex, Samogyi's sign, psychic depression, related especially to the evolution of the corpus luteum.

One must not confound these premenstrual crises or crises of the beginning of pregnancy with the reactional dyshyperthyroidism of the menopause, characterized by hot flashes, sweats, hypertension, paroxysmal tachycardia, palpitations and anxiety.

3. "*Hyperovaria*" (Dalché):<sup>61</sup> Precocious puberty, abundant menses, pain during and before the first day of the periods, intermenstrual leucorrhea, developed sexual instinct, variability of de-

<sup>58</sup> Dana et Berkeley, W., Med. Record, 10 mai, 1913; L. J. Kidd, Review of Neurology and Psychiatry, janv.-fév., 1913, pp. 1-24 et 55-75.

<sup>59</sup> Ce syndrome de Pellizi, Ogle, Oestreich et Slavyk, Frankl-Hochwart, Gutzeit, Hudovernig, Raymond et Claude, Marburg, A. Collin et Heuyer, R. Neurol., 30 mai, 1914, p. 729, serait lié à la destruction de la pinéale par une tumeur chez les enfants. Au contraire, par Gallais, la pineale semblerait avoir une rôle fonctionnel analogue à celui de la cortico-surrénale, loc. cit.

<sup>60</sup> L'adiposité pinéale de Marburg serait liée à un "hyperpinéalisme"?

<sup>61</sup> Dalché, L'hyper. et l'hypovarie, Gaz. des hôp., nos. 75 et 78, 1906. Je préfère dire dyshyperovarie.

sire depending on the menstrual period, well-developed eyebrows, thinness, pallor, large hips, rounded contour of the lower extremities, the size of which contrasts with that of the upper, lessened arterial pressure, uneasiness causing movement and action, nervous debility, tendency to loquacity, erotic crises.

## II. Testicles

1. *Infantilism*: Lack of development in the male genital organs, absence of secondary sexual characteristics, obesity, little hair, increased length of the lower extremities, smallness of the cranium, puerility.

2. *Acquired testicular insufficiency*.<sup>62</sup> Increase in size, decreased hairiness, rotundity of the figure, tendency towards obesity, increased size of the breasts, loss of desire, impotency, senility, increased arterial tension?, asthenia.

The types of testicular insufficiency are, according to Rebattu and Gravier:<sup>63</sup>

1. The sterile.
2. Eunuchoid giantism, because the internal secretion of the testicle was of late appearance. One notes in such a case a prolonged infancy.
3. Eunuchism by castration, characterized by giantism and a youthful aspect. The secondary sexual characteristics do not appear.
4. Revertive infantilism of Gandy, or the known asexual sort of state, with attenuation of the secondary sexual characteristics and a certain degree of obesity, due to delayed testicular disorder in the adult.
5. Dyshyperdiastematosi: short lower extremities, large head, plenty of hair, especially heavy moustaches, thinness, persistence of youth, no arterial hypertension, activity, moral and physical energy.

## 12. Prostate

1. *Prostatic insufficiency*: Asthenia, diminished potency, neurasthenia, sometimes suicide.

<sup>62</sup> La gerodermie génito-dystrophique de Rumno et Ferrannivi serait au testicules ce que le myxoedème acquis est à la thyroïde.

<sup>63</sup> J. Rebattu et L. Gravier, Étude des troubles de la sécrétion interne du testicule. Dissociation des secrét. int. et ext. du testicule. Retard de l'établissement de la secrét. int. Nouv. Iconographie de la Salpêtrière, juill.-août., 1913, pp. 257-271.

2. *Prostatic hypertrophy*.<sup>64</sup> Increased arterial tension,<sup>65</sup> slowing of the heart action, cerebral hemorrhage, genital excitement.

## B. POLYENDOCRINE SYNDROMES

### (a) *With Predominance of the Thyroid*

1. Basedovians, with hypertrophy of the thymus and vagotonic symptoms; scleroderma and tetany, amenorrhea; Addison's syndrome; acromegaly, etc.

2. Myxedematous cases with hypertrophy of the thymus, tetany, acromegaly, Addison's syndrome, amenorrhea, infantilism, hypertrophy of the breasts, etc.

3. Acromegalics or ovarian insufficients with varied disorders either psychic, nervous, vaso-motor, or trophic, entering sometimes into the myxedematous series and sometimes into the Basedovian.

### (b) *With Predominance of the Ovary*<sup>66</sup>

1. Thyroidal reaction to the ovarian insufficiency: tachycardia, palpitation, sweats, nervous irritability, vertigoes, scanty urination, tremors, anxiety, etc.

"One can no longer fail to notice," said I in 1908, "that the differences are very slight between these nervous manifestations and the picture of the attenuated forms of exophthalmic goiter. This pathogenetic idea allows of important therapeutic consequences. One can ask if it would not be of interest to institute an antibasedovian therapeutics, hemato-ethyroidin for instance, against the nervous and psychic disorders of the natural menopause, which recall trait for trait the symptoms of the Basedovian series."

Since then numerous successes of the sort have confirmed the justice of the idea.

2. Dyshyperovaria among cases of hypothyroidism:<sup>67</sup> anticipation, prolonged abundance of the menses, menorrhagia, metrorrhagia.

3. Thyro-ovarian disorders taken in the same sense: be it the ovarian insufficiency in the myxedematous series, or the dyshyperovaria in the Basedovian series, in all cases the nervous dis-

<sup>64</sup> Elle coïncide souvent avec l'insuffisance.

<sup>65</sup> L'extrait prostatique est hypotenseur et cardio-moderateur, Thaon. Soc. de biol., 13 juillet, 1907. Son injection est suivie de vaso-dilatation cérébrale. Ch. Dubois et L. Boulet, Soc. de biol., 19 avril, 1913, p. 811.

<sup>66</sup> Schickele, G., Kongress f. innere med., 1911.

<sup>67</sup> Leopold, Levi et H. de Rothschild, La petite insuffisance thyroïdienne, 1913, p. 153.

orders, whatever they may be, of the dysthyroidal women are modified by the ovarian rhythm at all times

*(c) With Predominance of the Pituitary*

1. Infantile giants with their clinical varieties: feminism, eunuchism, cryorchidism, pseudo-hermaphroditism of the feminine type, mental puerility.

2. Acromegalics with deficiency syndromes, myxedema, infantilism, amenorrhea, obesity, asthenia.

3. Acromegalics, who on the contrary have syndromes of hyperactivity, more or less vitiated either of coöperation or supply: simple or exophthalmic goiter, arterial hypertension and atheroma, lacteal secretion.

*(d) With Predominance of the Suprarenals*

1. Addisonians with amenorrhea, impotence, chilliness, tetany or, on the contrary, exophthalmic goiter.

2. And very often Basedovians, acromegalics, giants, with spontaneous glycosuria of alimentary or adrenal type, this latter being able in certain cases to cause one to presuppose a certain degree of suprarenal activity.

*(e) Without Marked Predominance*

Take the case of Claude and Gougerot: loss of sexual characteristics, senile face, thick skin, wrinkles, pigmentations, chilliness, absence of perspiration, asthenia, lowered arterial tension, tetany, atrophy of the testicles, of the prostate, of the suprarenals, thyroid and possibly of the parathyroids.

In order to include these nervous disorders revealed in the endocrine syndromes in one complete aspect, I have grouped them together under five headings, motor, sensory, vegetative, and psychic disorders, to which I have added the results of the sympatho-vagotonic tests.

These are:

1. Motility (tonus, sthenic, reflex, voluntary);
2. Sensibility (special, general);
3. Vago-sympathetic:
  1. The sense of conscious existence (general, hunger, thirst, genital);
  2. Lisso-motility (pupil, vaso-motor, pilo-motor, chromato-

- motor, lisso-motor properly speaking, arterial tension);
3. Cardiac rhythm;
  4. Digestive secretions (salivary, gastric, hepatic, pancreatic, intestinal), cutaneous (sweats), urinary (water, sugar); endocrinal.
  5. Eutrophia. General good nutrition.
4. Psychism: rhythm, response, emotion, attention, memory, intelligence, activity, sleep, instinct (sexual).
  5. Sympatho-vagotonic tests: adrenalin, atropine, eserine, pilocarpine, oculo-cardiac reflex.

Now, if I set aside the sympatho-vagotonic tests, then although it is very easy to answer plus or minus to different questions concerning the nervous state just analyzed, when one considers the thyroïdal syndromes, it is impossible to do the same clearly for the other syndromes. Those which furnish most of the definite answers after the thyroïdal syndromes are the ovarian syndromes. One single functional whole is affected by all, that is a sense of well-being (eutrophia); but I have indicated correctly that many of the disorders allied to endocrine dysfunction may be independent of the nervous system. Whence comes this first affirmation, that it is above all the thyroid syndromes and in the second place the ovarian syndromes that are most frequently accompanied by nervous disorders?

There is therefore an enormous difference between the endocrine glands viewed from the nervous consequences resulting from their disturbances.

Moreover the importance of the thyro-ovarian relations explains the differences according to sex of one portion of the neurology and especially of the psychiatry.

If, on the other hand, one classifies the divers groups of nervous disorders, psychic disorders appear to predominate in the thyroïdal syndromes, the vago-sympathetic disorders in the thyroïdal and ovarian syndromes, and finally the disorders of neuro-striated muscle motility predominate in the thyroïdal, parathyroïdal, thymic and suprarenal syndromes. Not only then are the endocrine syndromes far from being equal as regards wealth of nervous elements, but in addition they involve a relative election amidst these elements.

It remains to discover the reasons for these varieties of coincidence in delving further into the probable mechanism of their production.

After this very summary account of the facts, let us consider their interpretation.

Among the nervous symptoms—motor, sensory, vaso-motor, secretory, trophic and psychic—revealed in the enumerated endocrine syndromes, all the world admits that there are some that are caused by endocrine disturbances; thus tachycardia and active vaso-dilatation are caused by thyroidal disorders in Basedow's syndrome, as are asthenia and lowered arterial tension by suprarenal disorders in Addison's syndrome. These glandular disorders themselves may be in their turn secondary to a nervous disturbance. I will bring to your notice such cases in the succeeding chapter. This is not really the question. The endocrino-nervous relationship is demonstrated: endocrinogenous nervous disorders do exist.

Such is my first conclusion, universally admitted. This does not mean to say that in other respects all the nervous symptoms existing in individuals afflicted with an endocrine syndrome are attached to this syndrome and dependent upon the glandular disturbance of which it is the expression. In addition, among the nervous disorders which depend upon the disturbance, one must differentiate two groups according as to whether they are related directly or only indirectly.

The direct endocrino-nervous relationships have numerous examples, both clinical and experimental: tachycardia in Basedovians, hypotension in Addisonians, mydriasis following the conjunctival instillation of adrenalin, etc.

The indirect endocrino-nervous relationships are often extremely difficult to outline precisely, and it is in their study that one part of the difficulties of the question lies.

I will also divide these relationships into four categories.

The first category includes the indirect endocrino-nervous relationships through evolutionary morphological intervention. Thus a lesion of the thyroidal body sustained in early infancy, even in utero,<sup>68</sup> arrests the general development of the organism, and thereby interferes with the appearance of secondary sexual characteristics with all their consequences.

The glandular disorder, appearing in utero, in infancy or adolescence reacts on the development of the organism. The relationship comes essentially under the domain of ontogenesis and morphology. The secondary nervous disorders result from struc-

<sup>68</sup> J. Parhon, "Quelques considérations sur l'importance des fonctions endocrines, pendant la vie embryonnaire et foetale et sur leur rôle dans l'organogenèse," *Presse med.*, 1<sup>er</sup> oct., 1913.

tural anomalies, which are themselves secondary to the glandular lesion.

The second category, near neighbor to the first, includes indirect endocrino-nervous relationships through humoral morphological intervention. Thus normally the suppression of the ovarian function at the menopause entails well-known modifications of the female organism, the exaggeration of which determines, among other disorders, trophic symptoms such as a subcutaneous adiposity and development of hair. This example may also serve for the comprehension of a third category: the indirect endocrino-nervous relationships through a humoral intervention. The latter are extremely frequent; they are explained very naturally by the functional correlations under the influence sometimes of the hormones and sometimes, and perhaps more often, of the general modifications of metabolism (loss of calcium for example<sup>69</sup>) set free by the glandular disturbance or even directly by the cause of the latter.

For example increased arterial tension among Basedovians seems to be allied to the fact that their blood contains more adrenalin than that of normal individuals. Asher and de Rodt explain it by the fact that thyroïdal hypersecretion reinforces the action of adrenalin; by an indirect route the terminal organs of the sympathetic may be in a state of excitation, and as the secretory nerves of the suprarenals belong to the sympathetic, an increased secretion of adrenalin may result.

Per contra, to explain the tachycardia, one must invoke another factor besides the experiments, experience teaches only that the products of *normal* thyroïdal secretion augment the excitability of the autonomic nerves.

A fourth category is established by indirect endocrino-nervous relationships through nervous intervention. This intervention is excited at times physiologically and at other psychically. In the first case it consists for example of headache due to a meningo-encephalic vascular disturbance under the influence of a cervical sympathetic disorder of thyroïdal origin.

In the second case it consists for example of a phobia (fear of dying, of having heart disease, of becoming insane, etc.) determined by a diffuse anxiety allied to a menopausal tachycardia from excitation of the sympathetic of thyroïdal origin, and the accuracy of this mechanism is shown by the cure of such cases with hemato-ethyroidine (unpublished personal observations).

<sup>69</sup> Chiari et Fröhlich, Arch. f. exp. Pathol. u. Parmak., 1911, p. 214.

One can consider this last group, which is very important in psychiatry, as a fifth category, and speak of indirect endocrinonervous relationships, through psychic intervention. These relationships simply dogmatize the facts. They do not explain them. The Viennese school in a series of remarkable studies has attempted to interpret them. I will leave to my co-worker, Professor Biedl, the honor and pleasure of explaining these researches, which he partly instigated, and which he has had the wisdom to publish already with his collaborators and pupils, showing admirable command of the subject.

At the end of this analysis I will only remark that if the pharmacodynamic division of Langley, Eppinger and Hess of the vegetative system into the autonomic and sympathetic systems introduces in its own interest a new standard in the nomenclature of the nerves, up to now based on anatomy, and that if it is better now to think in terms of physiology rather than of anatomy, nevertheless the pharmacodynamic idea is not the whole of physiology, and the three present divisions of the vegetative system into the anatomical, physiological and pharmacodynamic do not fit their valencies together with any precision.

In a parallel manner to this division of the vegetative system Eppinger, Hess, Falta and Rudinger have divided the endocrine glands into two groups, one vagotrope and the other sympathicotrope. As I have already stated the vagotropes are the pancreas and parathyroids, and the sympathicotropes are the thyroid and the adrenals, to which Falta and Berterelli have added the infundibular portion of the pituitary. Now the analysis of nervous disorders in the endocrine syndromes shows moreover that the vagotonic and sympathicotonic disturbances, far from being always opposed to each other, exist at times in the same individual, not only consecutively but simultaneously, and accordingly there is not a simple and constant relationship between the endocrinal disturbance and the nervous disorder of one or the other group.

Things then seem much more complicated than one would have believed, and the classifications of the Viennese School, even if they have rendered, and still render, great service in arranging the phenomena, do not seem as yet sufficiently adequate in real truth to act as a basis for new systematizations.



## 2. Endocrine Disorders in Nervous Syndromes

In all individuals suffering with nervous diseases endocrine disorders may coexist; but I will only outline the cases in which these endocrine disorders may be under the direct or indirect influence of the nervous syndromes, or which play a rôle in determining the nervous symptoms, although their clinical manifestations are not evident. Following this point of view I will divide these syndromes into three large groups: sensory-motor, vegetative and psychic.

### A. SENSORY-MOTOR SYNDROMES

Among these syndromes there are a great number that can have nothing but a relationship of casual coincidence or a more or less mediate attachment. That is why I eliminate the hemiplegias, paraplegias, ataxias, muscular atrophies, vertigoes, tremors, athetoses, choreas, spasms, myoclonias, contractures, convulsions, myotonias, hypotonias, myatonias, neuralgias, distributed pains, migraines, paresthesias by evident organic affections of the nervous system, with known lesions of the nerves, of the spinal cord or brain, even though endocrinogenous toxic functional nervous disorders often exist coincident with nervous symptoms of an organic nature. Certainly as bearing on the subject, for example, are the hemiplegias due to hemorrhage of the optic thalamus, often allied with suprarenal hypertrophies (Frouin), and which readily appear to be due to increased arterial tension secondary to dyshyperfunction of the adrenals; in like manner the cerebral hemorrhages of the menopause, allied also to ovarian insufficiency by the intervention of sudden hypertensive shocks in the vasomotor ataxia of that critical period; as well as, although inversely, increased suprarenal secretion by excitation of the splanchnic in the course of tabetic crises (there are endocrine secretory crises just as there are exocrine); also aspongiocytosis in these same suprarenals subsequent to the incessant motor agitation in cases of chronic chorea or mania (unpublished personal notes); also those tabetics or cases of syphilis of the nervous system with myxedema, infantilism, tetany, etc., caused by concomitant syphilitic lesions of the nervous system and the glands. In the first two cases the relationship is too indirect and mechanical; in the two following the relationship is inverse, neurogenous, direct and indirect; in the last the coincidence arises from a co-effect of the same cause, namely syphilis, acting on two different parts of the body. One could multiply such examples without profit.

I will retain among the sensory-motor syndromes only those whose pathology is still disputed, and which appear sufficiently often in coincidence with endocrine disorders for the hypothesis of a relationship between cause and effect to be at least worthy of discussion.

Such are

1. Certain intermittent paraplegias: thyroid, parathyroids, thymus, suprarenals.
2. Periodic paralysis (Westphal).
3. Pseudo-paralytic myasthenia gravis (Erb-Goldflam):<sup>70</sup> thymus, parathyroids.
4. Myopathies:<sup>71</sup> thyroid.
5. Certain vertigoes: pituitary, suprarenals, ovaries.
6. Certain tremors: thyroid.
7. Certain choreas: thyroid, suprarenals.
8. Certain spasms.
9. Certain myoclonias.
10. Tetany: parathyroids.
11. Parkinson's syndrome:<sup>72</sup> parathyroids, thyroid(?), pituitary(?), ovary(?).
12. Epilepsy: thyroid.
13. Eclampsia: parathyroids.
14. Myotonias.
15. Congenital myatonia.
16. Hypotonia.
17. Acroparesthesia.
18. The cephalalgias: thyroid, ovary.
19. Migraine: thyroid.
20. Certain paresthesias.

In this résumé I wish to state that the sensory-motor syndromes coming under the precise heading of the chapter: endocrine disorders in the nervous syndromes have not been described, so to speak, but I have nearly always indicated nervous syndromes in which endocrine disorders should be looked for in order to understand them. I have been guided therefore more by the relative symptomatic importance of the nervous and endocrine manifestations than by the causal relationship. From this last point of view

<sup>70</sup> Tobias, Neurol. Centralbl., May 1, 1913, pp. 551-62.

<sup>71</sup> Oppenheim, H., Congrès de Londres, 1913.

<sup>72</sup> Sainton et Barré, Soc. de Neurol., 26 juin, 1913. R. N., 15 juill., p. 55. Parhon et Goldstein, Soc. des sc. mèd., Bucarest, 1909, 1910; Encéph., oct., 1912, p. 228.

I must distinguish at first the cases, few in number, where the endocrine symptoms are caused by nervous disorders, such as the endocrine insufficiencies described recently by Claude, in the train of the crises of Erb-Goldflam myasthenia, and later on the more numerous cases where the nervous symptoms are caused by endocrine disorders.

This subgroup is not to be confounded nevertheless with that of the nervous disorder in the endocrine syndromes, because in the latter there is a clearly outlined endocrine syndrome, while in the former there is merely an endocrine commotion. If they are confounded owing to their relationship of pathological causality, they are to be distinguished clinically in definite types, with, in addition, all their intermediates between them.

This having been stated, two remarks arise from the preceding résumé. It deals especially with syndromes having paroxysmal manifestations and with disorders bearing on qualitative variations of motility.

This rôle played by the endocrine glands in paroxysmal nervous manifestations did not escape a clever clinician like Léopold Lévi,<sup>73</sup> and he has proposed the name of endocrinolepsies for such paroxysmal syndromes, because they burst forth of a sudden, like an explosion (lepsy, λαμβανειν to seize) and they are subordinated to an endocrine disturbance.

The principal endocrinolepsies are, according to Léopold Lévi, ordinary migraine and ophthalmic migraine, ordinary asthma<sup>74</sup> and nasal asthma, muco-membranous enteritis, urticaria, relapsing edemas, periodic hyarthrosis, acute exacerbations in chronic rheumatism, paroxysms of gout, crises of grayness of the hair, crises of anxiety, acute paroxysmal goiter.

I feel that I can add certain convulsive, tetanic, paralytic and asthenic crises.

These crises, sudden, variable, relapsing, subject to disappearance through the use of simple organotherapy (most often thyroidal, sometimes adrenal) or complex, are as a rule dominated by the feminine sexual life.

According to Léopold Lévi the endocrine disorder is the pathological mordant which sensitizes centers already predisposed. In

<sup>73</sup> Léopold Lévi, Endocrinolepsies, leurs caractères généraux, Soc. de méd. de Paris, 9 janv., 1914, pp. 44-47.

<sup>74</sup> La crise hémoclassique initiale découverte par Widal et ses collaborateurs dans l'asthme, Rev. méd., juill., 1914, comme dans l'urticaire et l'hémoglobinurie paroxystique, Sem. méd., 1913, n'élimine pas le facteur nerveux réactionnel et ses connexions endocaines.

thyroidal endocrinolepsies, he claims a hyperthyroidal paroxysm which activates the nervous centers by a local vaso-motor blast. I might state with equal reason that it is a general law of the nervous system to respond in intermittent fashion to continuous stimulation.

Be that as it may I have continued to insist on the paroxysmal character of sensory-motor syndromes, such as tetany, myasthenia, migraine, which seem allied with endocrinal disturbances.

Secondarily I recall that the schema of Lundborg,<sup>75</sup> open to discussion from certain viewpoints, has the merit of synthesizing the physio-pathology of the thyroid and parathyroids and of showing the rôle played by the parathyroids in the neuro-muscular regulation. It is in this way that he connects tetany, paralysis agitans, myoclonia (myoclonus, epilepsy), myotonia, with a parathyroid insufficiency, and pseudo-paralytic myasthenia and periodic myatonia with a hyper or dysfunction of the parathyroids.

Tetany is alone to-day no longer in doubt, as far as the other affections are concerned—it is nothing but an hypothesis as yet. The most firmly established hypothesis appears in relation to Parkinson's syndrome. In this instance as Roussy and Clunet<sup>76</sup> state the parathyroids may be found in a condition of hyperplasia. As to the relation of this condition with the syndrome, it is ignored. It is quite possible, according to Claude,<sup>77</sup> that it consists of a simple reaction of defense in the organism.

### B. VEGETATIVE SYNDROMES

In this enumeration I will follow the plan of my *Pathology of the Sympathetic*<sup>78</sup> now being published.

#### (a) Tegumentary Syndromes

1. Local syncope of the extremities: thyroid, suprarenals, kidney.
2. Acrocyanosis: thyroid, thymus.
3. Erythromelalgia: ovaries, thyroid, suprarenals.<sup>79</sup>
4. Acroparesthesia: suprarenal.
5. Erythema: thyroid.
6. Urticaria: thyroid.<sup>80</sup>

<sup>75</sup> Lundborg, *Deutsche Zeitschr. f. Nervenheilk.*, Bd. XXVII, 1904, p. 217.

<sup>76</sup> Roussy et Clunet, *Arch. de méd. exp.*, 1910, no. 3.

<sup>77</sup> H. Claude, *Soc. de Neurol.*, fév., 1910.

<sup>78</sup> M. Laignel-Lavastine, *Pathologie du Sympathique. Esquisse d'anatomophysio-pathologie clinique*, 1 vol. in-8 de 600 p., Paris, Alcan, 1915?

<sup>79</sup> Moleen, G., *Journ. Amer. Med. Ass.*, 17 août, 1912.

<sup>80</sup> Les modifications sanguines qui précèdent la crise d'urticaire, ses rapports avec l'anaphylaxie, sa cause déterminante ramenée par Widal et ses

7. Dermographia: thyroid.
8. Purpura: liver.
9. Pruritus: liver, kidney, thyroid.
10. Melanoderma: suprarenal, thyroid.
11. Vitiligo.
12. Hyperidrosis: ovaries.
13. Chromidrosis.
14. Seborrhea: thyroid(?), testicles(?), ovaries(?).
15. Goose flesh: thyroid(?).
16. Premature grayness of the hair: thyroid.
17. Alopecia: thyroid.<sup>81</sup>
18. Hypertrichosis: thyroid, suprarenals, testicles, ovaries.
19. Zona and herpes.
20. Scleroderma: thyroid.
21. Raynaud's gangrene: thyroid(?).
22. Acute angioneurotic edema: thyroid.
23. Trophedema: thyroid(?), pituitary(?).
24. Adiposity: pituitary, thyroid, ovary, pineal.

*(b) Osteo-articular Syndromes*

26. Acromegalia: pituitary.

*(c) Syndromes of the Neuraxis*

29. Syndromes of the cervical sympathetic: thyroid(?), suprarenal.
31. Mydriasis: thyroid.
32. Myosis: suprarenal(?).
33. Glaucoma.
34. Glittering eye: thyroid.
35. Exophthalmos: thyroid.
36. Migraine: thyroid, ovaries.
37. Cephalic vaso-dilatation: ovaries(?).
38. Epilepsy: thyroid, ovaries.
39. Vertigoes: suprarenals, ovaries, thyroid.
40. Euphoria: thyroid.
41. Melancholia: thyroid, suprarenals, ovaries.
42. Anxiety: thyroid, ovaries.

élèves (Widal, Abrami et Et. Brissaud: L'auto-anaphylaxie, Sem. méd., 24 dec., 1913), à un conflit entre colloïdes, n'excluent pas l'importance de la thyroïde dans les prédispositions réactionnelles et les manifestations neuro-cutanées.

<sup>81</sup> Sabourand, Ann. de dermatol., mars, 1913.

*(d) Circulatory Syndromes*

- 43. Vascular spasms: suprarenals.
- 44. Increased arterial tension: suprarenals, pituitary.
- 45. Vaso-dilatations: thyroid, ovaries.
- 46. Arterial hypotension: suprarenals, pituitary.
- 47. Palpitations: ovaries, testicles, thyroid.
- 48. Tachycardia:<sup>82</sup> thyroid, ovaries.
- 49. Bradycardia: pituitary (?).
- 50. Arrhythmia.
- 51. Cardiac neuralgias.
- 52. Syncope: thymus, suprarenals.

*(e) Respiratory Syndromes*

- 54. Asthma: thyroid.
- 56. Acute edema of the lungs: suprarenals.
- 57. Rhinorrhea.

*(f) Digestive Syndromes*

- 58. Hypersalivation.
- 60. Gastric crises.
- 61. Enteralgic crises; thyroid.
- 65. Digestive atony.
- 66. Digestive spasms.
- 71. Diarrhea.
- 72. Glycosuria: thyroid, suprarenals, pancreas, liver, pituitary.
- 78. Constipation: thyroid, pituitary.
- 80. Muco-membranous entero-colitis: thyroid.

*(g) Urinary Syndromes*

- 84. Polyuria: pituitary(?).
- 85. Albuminuria.
- 89. Too frequent urination: thyroid.

*(h) Genital Syndromes*

- 95. Impotency: prostate, testicles.
- 96. Priapism: suprarenals.
- 98. Ovarian crises.
- 101. Frigidity.
- 104. Menstrual troubles: thyroid, ovaries.

<sup>82</sup> La théorie endocrine de la tachycardie paroxystique a été exposée par Savini (Arch. des mal. du coeur, nov.-déc., 1912). J'en ai confirmé l'authenticité chez une femme à la ménopause qui guérit par opothérapie ovarienne.

*(i) Endocrine Syndromes*

- 105. Basedow's syndrome: thyroid, thymus.
- 106. Addison's syndrome: suprarenals.
- 107. Polyendocrine sympathetic syndromes.

*(j) General Trophic Syndromes*

- 108. Hyperthermia: thyroid.
- 109. Hypothermia: thyroid.
- 111. Diabetes mellitus: pancreas, suprarenals.
- 112. Emaciation: ovaries, testicles, thyroid.
- 113. Obesity: thyroid, pituitary, pineal, ovaries, testicles.
- 114. Herpetism: thyroid.

All these vegetative nervous syndromes are the functional results of very different causes. Such glands as I have marked opposite to them simply indicate that in certain cases the endocrine disorders, which have been noted in coincidence with the nervous disorders, have played a rôle in the determination of these nervous syndromes, or that inversely the endocrine disorders are secondary to the nervous commotions.

In fact it is often very difficult clinically to keep from confusing the angio-tropho-neuroses and their endocrinal consequences with the endocrinopathies and their vegetative nervous consequences.

Quite often the symptomatic intricacy and the paucity of chronological and established data are such that one is forced to have recourse to a synthetic expression, such as *sympathosis*,<sup>83</sup> which I have proposed, and which simply indicates a vegetative nervous syndrome. Among the univocal sympathoses, the sensory, circulatory, lisso-motor, secretory and trophic sympathoses constitute the framework for the preceding facts. I must call attention to the considerable rôle that these vegetative nervous syndromes play in dermatology in their vaso-motor, secretory and trophic types and in psychiatry in their cenesthetic and vaso-motor types.

It is here that one grasps the closeness of the connections between the internal secretions and the vegetative nervous system, and one understands thereafter the interest of the study of the sympathetic and the vascular glands in domains like dermatology and psychiatry,<sup>84</sup> where taken clinically they still conform partly to a botanical classification.

<sup>83</sup> Laignel-Lavastine, *Les sympathoses*, Presse méd., sept. 20, 1913.

<sup>84</sup> Laignel-Lavastine, *Le sympathique et les viscères dans les affections mentales*, *Traité internat. de Psychol.-pathol.* Dans ce travail je montrais l'importance de ce que Münzer nomme très heureusement "la décentralization de la psychiatrie."

Just as I have laid stress elsewhere<sup>85</sup> on the rôle of the sympathetic in that which I have called the pathology of the border made up of those humoral reactions or reflexes saddled on neurology, dermatology, psychiatry, visceral medicine and the pathology of metabolism, one can claim that there is a whole endocrino-vegetative chapter still to be written in dermatology, as in digestive, circulatory, respiratory, urinary and mental pathology.

### C. PSYCHIC SYNDROMES

My report<sup>86</sup> in 1908 at the Congress of Dijon on psychic disorders due to disturbances of the glands of internal secretion, the excellent report of Professor Parhon<sup>87</sup> at the Congress of Gand in 1913 on the glands of internal secretion in their relationship to psychology and mental pathology and the recent article of M. Van der Scheer<sup>88</sup> have outlined and brought out the question.

In order to avoid criticism I refer to their works and enumerate the results which are the least doubtful.

#### (a) *Syndromes of Cerebral Debility*

1. Anencephalia: suprarenals.
2. Idiocy and cranial malformations:<sup>89</sup> thyroid, parathyroids, suprarenals.<sup>90</sup>
3. Imbecility.
4. Backwardness:<sup>91</sup> thyroid, pituitary, ovaries, testicles, thymus.
5. Mental debility.
6. Psychic imbalance.<sup>92</sup>

#### (b) *Syndromes of Delirium*

7. Mania:<sup>93</sup> thyroid, suprarenals, ovaries.
8. Melancholia: thyroid, ovaries, liver, suprarenals, kidneys, pituitary.

<sup>85</sup> Laignel-Lavastine, Définition du sympathique, *Gaz de Hôp.*, 1912.

<sup>86</sup> Laignel-Lavastine, Congrès des aliénistes et neurologistes, Dijon, 1908.

<sup>87</sup> C. I. Parhon, III<sup>e</sup> Congrès internat. de Neurol. et de Psychiatrie, Gand, 1913.

<sup>88</sup> W. M. Van der Scheer (de Meerenberg), Die pathogenetische, Stellung der Blutdrüsen in der Psychiatrie, Jahresversammlung der Nederlandsche Vereeniging voor Psychiatrie en Neurol., 3 juill., 1913.

<sup>89</sup> Bertolotti, *Presse méd.*, 2 mai, 1914, p. 334.

<sup>90</sup> Guilorowsky, Influence d'hypoplasie surr. sur ce cas d'idiotie, Congr. assist. des aliénés, Moscow, janv., 1914, *Arch. de Neurol.*, mars, 1914, p. 163.

<sup>91</sup> Hastings-Gilford, Influence des glands a secret. int. sur le développ., Congr. internat. de Londres, 1913, sect. de Psychiatrie, rapp.

<sup>92</sup> Cot. Ch. et Dupin, Insuff. glandul. et anormaux, *Enceph.*, mars, 1913, pp. 223-34.

<sup>93</sup> Lafora, G. R., Folie manique depressive et hyperthyroidisme, *Revista clin. de Madrid*, 15 oct., 1913, pp. 294-301.



9. Mental confusions: liver, kidneys, thyroid, parathyroids, pancreas, pituitary, suprarenals, ovaries, testicles.
10. Systematized hallucinatory deliria.
11. Systematized deliria without hallucinations.
12. Genital perversions: ovaries, testicles, prostate, suprarenals.

*(c) Syndromes of Dementia*

13. General paralysis: suprarenals, thyroid, pituitary, etc.
14. Dementia præcox:<sup>94</sup> testicles, ovaries, pituitary.
15. Cerebro-arteriosclerosis: suprarenals, testicles.
16. Senile dementia: parathyroids, thyroid, testicles, ovaries.
17. Epileptic dementia.

*(d) Neuro-psychic Syndromes*

18. Epilepsy: thyroid, parathyroids, testicles, ovaries.
19. Nervosism: thyroid.
20. Hysteria: thyroid, ovaries.
21. Neurasthenia: suprarenals, testicles, ovaries.
22. Psychasthenia: thyroid, ovaries, testicles, suprarenals.

This analysis of endocrine disorders investigated, discovered or supposed, in the psychic syndromes allows in the first place the conclusion that just as psychic symptoms are met with frequently in endocrine syndromes, so are endocrine disturbances indicated very often in the psychic syndromes. Moreover one should state that the value of the indicated endocrine disorders is very uncertain, and the confirmation of a clinical endocrine sign or glandular test is vastly more important than an organotherapeutic result and above all more important than the existence of endocrine lesions, because we know the utter banality of all these.

The frequency of pathological endocrino-psychic associations are not explicable alone by fortuitous coincidences and more or less mediate attachments. It seems to me necessary to admit, in certain cases at least, a relationship of casuality. This conclusion which I advanced in 1908 has been confirmed by numerous authors, and recently by M. Parhon in 1913. This relationship of casuality varies moreover according to the case. Eliminating fortuitous coincidence I will sum up in a few lines my ideas on the more or less mediate bonds between endocrine and psychic disorders, on the causal rôle played by the psychic syndromes in endocrine disorders

<sup>94</sup> Dercum et Ellis, J. of Nerv. and Mental Disease, fev., 1913, pp. 73-90.

and on the causal rôle played by the endocrine disorders in the psychic syndromes.

### 1. RELATIONSHIPS OF CONNECTION BETWEEN ENDOCRINE AND PSYCHIC DISORDERS

In this heterogeneous group I place the cases in which the frequency of association between endocrine and psychic disorders makes one think that it consists of something more than a coincidence, and in which nevertheless one can not demonstrate a clear relationship of casuality.

Thus psychic excitations give rise to fits of rage or anxiety. In a similar way to psychic changes, modifications of endocrine secretion, thyroidal for example, appear to me to be among the factors that make up that physio-psychic complex called emotion. Some think that the psychic factor is causal, others like Redmond and Sauvage<sup>95</sup> think that "the phenomenon of emotion is the result of auto-intoxication, due to a sharp destruction of endocrine equilibrium." I consider that the mechanism is a triple one: at times the psychic act releases the secretory act, at others the endocrine act releases the psychic act, and at still others the endocrine and psychic action are both the coresults of the same cause. It consists of a proximate adherence.

Take for another example a given case of juvenile general paralysis with infantilism. The meningo-encephalitis like the atrophic thyroidal sclerosis, being the results of hereditary syphilis, are both coeffects of the same cause. The two syndromes, psychic and endocrinal, are therefore bonded by a relationship of mediate adherence.

### 2. CAUSAL RÔLE OF THE PSYCHIC SYNDROMES ON THE ENDOCRINAL DISTURBANCES

In the normal state one can not deny that psychic excitations determine disorders of secretion. The experiences of Dumas and Malloizel and the results of Cannon, where emotion has increased the quantity of adrenalin in the blood, like the classic case of Trousseau of exophthalmic goiter caused by a fit of rage, are instances of the kind.

In the pathological state the results are the same: motor agitation caused by delirium may bring about almost complete aspongocytosis of the suprarenals, as I have had occasion to observe in the insane. It is therefore plain to me that the psychic factor may

<sup>95</sup> Redmond and Sauvage, Soc. de psychiatrie, 10 fev., 1913.

bring about the endocrinal result. Moreover the psychogenic mechanism of endocrinal disorders is not uniform, and if in certain cases it is directly psycho-secretory, it is much more frequently indirectly psycho-physio-secretory, the intermediary perhaps being the physico-chemical modifications of divers viscera of life of relationship or of nutrition.

### 3. CAUSAL RÔLE OF ENDOCRINAL DISORDERS ON THE PSYCHIC SYNDROMES

This rôle, by far the most important, is not always uniform. One can differentiate three large divisions as I have already shown in 1908.

1. Sometimes the endocrinal disorder arising in utero, in infancy or adolescence reacts on the development of the organism and the brain: the psychic disorders result from anomalies of structure.

2. At others the endocrine disorder, compatible with existence and a relative functioning of the organism, brings about in organic as well as psychic life more or less reciprocal modifications of various modalities.

3. At still others the endocrine disorder no longer moderate but massive produces, along with grave disorders of the organism, intense cerebral reactions, which reveal themselves always in the same way by classical toxic psychoses of the mental confusion type.

These three divisions seem to me to explain the facts of the third group with sufficient connection.

1. The first is the most simple. It remains essentially in the domain of ontogenesis and morphology. The mental puerility of infantilism is an example.

2. The second is on the humoral order. The internal organs being specifically modified by the elective disturbance of one or many of the selected internal secretions, the anatomical elements which they bathe are by such modified in their vitality. There result accordingly pathological changes along with somatic, anatomic and functional alterations. The former like the latter, reflexes of a like humoral disorder, present a debased series of a frank pathology or normal model.

With greater precision, one can differentiate with Parhon three varieties in the humoral action of the endocrine glands on the psyche.

In the first place these glands directly influence the nervous

system itself, and one can distinguish, with Munzer, sympathico-tonic, vagotonic (or better autonomotonic) and polytonic glands, these last being able to affect, for example, the cerebral cortex, the autonomic system and the sympathetic. The tonicity of one or many cortical centers being influenced, their psychic function will thus remain the same. However, this psychic function will respond equally to changes in the cerebral circulation, the state of the respiration, the oxidation of the body, and the chemical composition of the blood—for example the richness or poverty in calcium salts, etc. Now one or the other of these influences, if not all, are affected by the sympathicotonic or autonomotonic action of the endocrine glands.

Side by side with this action, more or less directly central, Parhon claims a peripheral action "which moreover may be itself partly the consequence of a central action"; it is the action of the endocrine glands on the sense of conscious existence.

He adds that "the action of the genital glands must acknowledge partly at least a similar mechanism." Finally the endocrine glands, by their action on the general metabolism, bring about modifications of different tissues, which affect the psyche through humoral, nervous reflex or psycho-cenesthetic means.

3. "Finally, I claimed, the third mode of action, the massive, of the endocrine disorders on the mental life, which is characterized by toxic psychoses, is often very complex in the sense that the cerebral intoxication is not only the result of the disturbance of the incriminated gland, caused by the concomitant syndrome, but the result of a series of associated or secondary functional insufficiencies. It is thus that in cases of Addison's disease with delirium the discovery of azotemia by Sicard and Haguenau<sup>96</sup> might give rise to the hypothesis that renal insufficiency may have been added to the suprarenal insufficiency in the mechanism of delirium, but the statement must be made that the determination of azotemia has no interest unless such is not terminal, because of its known frequency immediately before death.<sup>97</sup>

In a word the endocrine disorders in nervous syndromes, whether they have been established by clinical or anatomical methods or induced by physiological or therapeutic proofs, are face to face with the nervous syndromes.

1. It may be a relationship of simple fortuitous coincidence.
2. It may be a relationship of more or less mediate adherence.

<sup>96</sup> Sicard et Haguenau, Soc. méd des Hôp., 15 mai, 1914, p. 902.

<sup>97</sup> D. Dumitresco et A. Popesco, Presse méd., 27 juin, 1914, p. 487.

3. It may be a relationship of causality: at times the nervous disorder has determined the endocrine disturbance, at others and inversely it is an endocrine disturbance which has determined the nervous syndrome, but the frequent clinical latency of the former may interfere with the comprehension of the cause of the latter.

It is necessary to remember that to a patent nervous disorder there is frequently attached a latent endocrine cause. One should therefore look for an endocrine cause in any nervous syndrome of an unknown or obscure origin. But one must not be determined to find such in spite of everything, and to accept contingencies for necessities.

In conclusion, all the facts gone over in this critical review are explained aside from coincidence and coeffects of the same cause, at times by a direct or indirect endocrino-nervous relationship through a morphological intermediary (evolutional or humoral) or a physiological intermediary (humoral or nervous) or a psychic intermediary, at others by a direct or indirect neuro-endocrinal relationship through a direct morpho-evolutional, physiologic reflex or psychic intermediary or through the same indirectly (motor activity, general nutrition), and at still others by recurring endocrino-neuro-endocrinal relationships and neuro-endocrino-psychic relationships.

This is explained in the following table.

#### ENDOCRINO-NERVOUS RELATIONSHIPS

A. Coincidence.			
B. Connection.	{	Proximate.	
C. Causality.		Mediate.	
1. Simple...	{	1°. Endocrino-nervous.	
		(1) Direct.	
		(2) Indirect through intermediaries.	{
2. Double...	{	2°. Neuro-endocrinal.	
		(1) Direct.	
		(2) Indirect through intermediaries.	{
3. Double...	{	3°. Endocrino-neuro-endocrinal.	
		4°. Neuro-endocrino-nervous.	

### B. ENDOCRINO-NEUROLOGICAL SKETCH

In practice, that which matters is less the neurogenous endocrine disorders than the endocrinogenous nervous disorders.

Of course the endocrine disorders secondary to the nervous disorders are very interesting theoretically and practically. Theoretically they show the unity of human personality and not only the influence of nervous disorders on the secretions and nutrition, but in addition, to use an old expression which illustrates the picture, the mastery of the soul over the body.

Practically their interest is twofold, because attenuated and masked by the nervous syndrome, they may nevertheless modify and complicate it, as can be seen in certain tabetics and general paralytics. Inversely when very marked they may mask more or less through their symptomatic richness the clinical expression of the nervous disorders which cause them, and thus effect a change with an endocrine syndrome which is clinically primitive. This is the case in certain Addisonian and Basedovian syndromes, which are not originally endocrinogenous but neurogenous.

Endocrinogenous nervous disorders, which are infinitely more frequent than neurogenous endocrinal syndromes, form altogether an extremely important group, which, unburdened with morphologic and endocrinogenous trophic syndromes in which a nervous factor is not constant, constitute the greater part of functional neurology.

I intend in this sketch, as a practitioner, to limit myself almost entirely to that which functional neurology owes to endocrinology.

I will take my illustrations from certain ordinary symptoms, endocrino-vegetative syndromes, traditional psychoneuroses, temperaments and characters.

#### I. ORDINARY SYMPTOMS

Among the ordinary symptoms I retain arbitrarily asthenia, headache, insomnia, anxiety, sweats, constipation, arterial hypertension and obesity in order to show that there are for each of these symptoms certain cases which arise from an endocrinal cause, and that daily one should give an endocrine factor consideration in pathogenic diagnosis. It should be considered but not determined upon except on the authentication of well-marked signs, that is to say, clean cut and frank. Moreover most frequently such consideration ends in elimination.

## (I) ASTHENIA

Asthenia is abnormal fatigue. It is either general or more especially motor or psychic.

Motor asthenia is an extremely commonplace symptom, due to various causes, either infectious, toxic or psychic.

Among the motor asthenias of endocrinal origin, the first to be recognized was the asthenia of Addison's disease. It is connected with adrenal insufficiency, and is accompanied by arterial hypotension.

In addition there are motor asthenias allied with adrenal insufficiency, which are not Addisonian. This fact is well known to-day. They are very common and are usually but not always accompanied by arterial hypotension.

Their recognition and consequently their organotherapeutic treatment will permit the cure of a large number of sick, ticketed as neurasthenics, cyclothymics, melancholics and even hypochondriacs. Certain cases of arteriosclerosis with hypotension enter into this category. The interesting point is that they were often asthenics already at the beginning of their arteriosclerosis, while they still had hypertension. This asthenia of hypertensive arteriosclerotics existing from the beginning is well understood to-day. Maurice de Fleury among the first has shown its frequency. In such cases there is often a dyshyperfunctioning of the suprarenals. This asthenia of hypertension through dyshyperfunction may be recovered from completely through a simple regime. It can after a period of years border on asthenia due to adrenal insufficiency, an insufficiency itself secondary to the old glandular hyperfunction and without mechanical participation of cardiac insufficiency; I have followed a lot of such cases in the last ten years.

The majority of endocrinogenous muscular asthenias are suprarenal, but there are others which are thyroïdal, thymic, parathyroïdal, pituitary, ovarian, testicular and polyglandular.

Dejerine and Gauckler<sup>98</sup> have brought the weight of their authority to the support of these data.

The endocrinal origin of a muscular asthenia having been recognized, diagnosis is not complete. The cause must be determined. In the simple cases it is sometimes an infection (a beginning tuberculosis, convalescence from grip or diphtheria, etc.), at others an intoxication. In the more complicated cases it is a vascular, nervous or psychic disturbance, under the subjection itself of a previous endo-

<sup>98</sup> Dejerine et Gauckler, *Les asthénies périodiques crises de fatigue*. Presse méd., 17 juin, 1914, pp. 457-459.

crinal disorder. It is often like this in the hypophysics of Martinet,<sup>99</sup> a typical case of which I have actually seen, which merits publication by itself.

An important fact is that the asthenia may be not the result but the cause of an endocrinal insufficiency. Claude<sup>100</sup> believes this to be the case in the paralytic myasthenia of Erb-Goldflam. According to him the endocrine glands are normal or rather increased in size, but they are exhausted by an effort truly excessive. This is brought about by the entrance into the circulation of poisons to the nerve and muscle cells of inconstant origin, but which, in certain cases, arise from a disordered thymus. In the Erb-Goldflam syndrome the multiple insufficiency of the endocrine glands by functional exhaustion is therefore secondary, just as the disappearance of spongiocytes in the suprarenal cortex is secondary to an intense or prolonged muscular agitation. I have had occasion to confirm in eight cases this fact grasped experimentally by Mulon<sup>101</sup> and clinically by Porak.<sup>102</sup>

## (2) HEADACHE

Not only migraine,<sup>103</sup> but the most ordinary headache may be of endocrinal origin. Many of the headaches called neurasthenic come under this heading. The most frequent of the endocrinogenous headaches are those of thyroidal<sup>104</sup> origin. As a general thing slight concomitant signs of hypothyroidism, such as palpebral edemas, anorexia, constipation, somnolence, chilliness, muscular and articular pains assist the diagnosis; but sometimes the thyroidal disorder does not reveal itself except by the headache, which of itself and through causal elimination should possess an indicative value. These headaches are very frequent among women; are more or less governed by genital life, improved by sexual relations<sup>105</sup> and cured by pregnancy. I have gathered typical cases of the kind in my practice.

<sup>99</sup> Martinet, Syndrome hypophysique, *Pr. méd.*, 21 déc., 1912. S. hypophysie et insuff. plurigland., *Ac. de méd.*, 22 avril, 1913, et *Pr. méd.*, 2 août, 1913.

<sup>100</sup> H. Claude, La myasthénie paralytique et les syndromes asthéniques par insuffisance surrénal, *Acad. de méd.*, 9 juin, 1914, et *Soc. de Neurol.*, 28 mai, 1914. *R. N.*, 15 juin, p. 786.

<sup>101</sup> Mulon, P., *Soc. de biol.*, 26 juill., 1913, p. 189.

<sup>102</sup> Porak, *Mém. inéd.*

<sup>103</sup> Léopold Lévi et H. de Rothschild, *Acad. de méd.*, 14 nov., 1911, p. 22; *Répertoire de méd. int.*, mars, 1912; Goett, La migraine thyroïdienne, *Th. Bordeaux*, 1909. Flatau, La migraine, *Berlin*, 1912; A Véron, *id.*, *Th. Lyon*, 1914.

<sup>104</sup> Gaujoux, Céphalée hypothyroïdienne et opothérapie, *Soc. des Sc. méd. de Montpellier*, 14 mars, 1913; Bilancioni, G., *Il Policlinico*, sez. pratica, 23 mars, 1913, pp. 401-6.

<sup>105</sup> Migraines de jeunes filles guéries par le mariage, migraines de jeunes femmes absentes le lendemain de l'accomplissement des devoirs conjugaux.



After the thyroidal types, the ovarian, testicular, pituitary, suprarenal and polyendocrinal headaches are to be noted.

### (3) INSOMNIA<sup>106</sup>

Among the insomnias those of Basedow's syndrome and the menopause, which come under the heading of dyshyperthyroidism, show the existence of endocrinogenous insomnias.

The most frequent of these is the dyshyperthyroidal, seen clearly in the cases that I have just cited. It is probably present in many of the psychoses, where one knows that thyroidal excitation is frequent. It is to be suspected at least in the "nervous" where no other appreciable cause justifies its presence.

The insomnia of acquired ovarian insufficiency seems to contradict this precedent.

Perhaps it conforms to the same lines as the insomnia of certain cases of hypertension of the fifties, where the genital functions are lessened.

### (4) ANXIETY

The anxiety of Basedovians and of many women at the menopause and its cure by hematothyroidin, confirmed many times by Alquier, Rose, myself and many others, show the existence of endocrinogenous anxiety due to dyshyperthyroidism. This anxiety seems really to be that of the anxious melancholias. It is already known that the works of Parhon tend to show the rôle played by the thyroid in what he calls the affective psychoses.<sup>107</sup>

The anxiety frequently noted in acquired ovarian insufficiency seems to be controlled by the same mechanism.

Clinically considered, all anxiety that does not possess warrant should make one suspicious of an abnormal excitation of the thyroid.

### (5) SWEATS

A vagotonic reaction, released by pilocarpine, arrested by atropine, the sweats which come on in crises at the menopause, are associated in the hot flushes with active vaso-dilatation, but may be present alone. Symptomatic in this instance altogether of acquired ovarian insufficiency and of thyroidal reaction, they are seen in the two conditions. We are all familiar with the frequent sweats of Basedovians.

<sup>106</sup> A. Salmon, *La fonct. du sommeil*, Vigot, 1910.

<sup>107</sup> Cette voie permettra peut être de trouver des raisons aux intermittences de toutes des syndromes d'excitation et de dépression, maniaques et mélancholiques.

According to this there are endocrinogenous sweats due to dyshyperthyroidism. This vagotonic expression referable to thyroidal excitation is associated very often with sympathicotonic manifestations of a similar origin. It is thus in the classical hot flushes of the menopause.

#### (6) CONSTIPATION

Spastic constipation, "vagotonic," which yields to belladonna, is a nervous symptom.

Its recognition in cases of hyperchlorhydria, in certain neurasthenics, in women at the menopause or at the beginning of pregnancy, permits of cures as easy and complete as they are brilliant, through the use of the well-known belladonna pillule of Trousseau and Pidoux.

Then again it is frequently caused by ovarian or testicular insufficiency with abnormal excitation of the thyroid, as seen in the observations of Marañón.<sup>108</sup>

This constipation must be carefully distinguished from the constipation of myxedema, from the general type of constipation, such a common sign of hypothyroidism, and which is cured by organotherapy.

Thus the same symptom in its gross clinical expression may be of thyroidal origin, and point nevertheless to two different mechanisms, excitation or insufficiency of thyroidal secretion. This instance of thyroidal constipations is not the only example of endocrinogenous constipations that can be given. There appears to be one also of pituitary origin, although the cure of certain atonic constipations by the extracts of the posterior lobe of the pituitary does not demonstrate the nature of this, inasmuch as these extracts act as excitants of unstriated muscle tissue by virtue of their pharmacodynamic properties, and not on account of their elective vicarious or stimulating<sup>109</sup> action on the pituitary.

#### (7) ARTERIAL HYPERTENSION

To Vasquez belongs the credit for having described in man "arterial hypertension due to hypersecretion of the suprarenals," which Josué confirmed by experiments. In advance of this permanent hypertension, hyperadrenal secretion may show itself through hypertensive crises, which have been classical since the time of Pal. Moreover, there are other hypertensive crises besides the endocrinogenous,

<sup>108</sup> Marañón, G., *Hyperchlorhydrie et hyperthyroïdisme*, *Revue de méd.*, 10 mars, 1914, pp. 161-83.

<sup>109</sup> Hallion, loc. cit.

and among the latter others besides those due to hyperadrenal secretion. Those which are allied with disturbances of the pituitary, ovary, testicles, prostate, thyroid and parathyroids, have been recognized. In like manner there are permanent arterial hypertension which are not endocrinogenous, and among the latter some which are not of suprarenal origin.

There is no need to continue. I have simply tried to show that there are arterial hypertension which are nervous endocrinal syndromes, because they depend upon a vascular spasm, of endocrinal origin.

### (8) OBESITY

The existence of endocrinogenic obesities is no longer a matter of dispute. Mouriquand<sup>110</sup> has described them well recently in children.

I have reported several cases myself this last year.<sup>111</sup>

The only point of interest is the demonstration of a nervous factor in the determination of these endocrinogenic obesities. In the majority of cases I do not think that this exists, but believe that such obesities arise through humoral disturbance of endocrinal origin. Nevertheless a nervous factor is present in the cases noted where a cerebral tumor gives rise to obesity through pressure on the pituitary. One might also suspect, if not prove, a nervous factor in those cases of segmentary<sup>112</sup> or paraplegic disposition of adipose tissue. I have with Viard reported a case of this type, which corresponding to a trophedema of Henry Meige, studied previously with M. Sicard,<sup>113</sup> caused me to view in their entirety "the variations of the panniculus adiposis, according to the divers physiological conditions—of infancy, puberty, pregnancy, lactation, castration, and of the menopause—and to pathological conditions—of the simple or associated endocrinal syndromes, thyroidal, pituitary, ovarian, testicular, suprarenal, and parathyroidal—pursuant to their relations with the trophedema of Henry Meige, the adiposis dolorosa of Dercum, the intermediate affections between these two syndromes, to

<sup>110</sup> Mouriquand, *Congres de Pédiatrie*, Rapp., 1913.

<sup>111</sup> Laignel-Lavastine et L. Boudon, *Obésité par sarcome juxta-hypophysaire*. Soc. méd. des hôp., 13 fev., 1914; Laignel-Lavastine et Pitulesco, *Obésité familiale avec perturbations endocrines*, *id.*

<sup>112</sup> Sicard et Berkowitsch, *Adipose dou. par insuff. ovarienne*, *Gaz. des Hôp.*, 1908, p. 848; Claude et Sézary, *Adip. dou. aet remarquable de l'opoth. Thyr.*, *Gaz. des Hôp.*, 1913, No. 86, p. 69; Ivanoff, *Mal de Dercum*, *R. russe de Psychiatrie*, mars, 1913; Weber, Parks, *Lipodystrophie progressive*; R. Hirschfeld, in *Handbuch der Neuro. de Lewandowsky*, Bd. IV, pp. 455-71.

<sup>113</sup> Sicard et Laignel-Lavastine, *Un cas de trophoedème acquis*, Soc. de Neurol., 15 janv., 1903, *Nouv. Iconographie de la Salp.*, janv., 1903.

certain states of hardening of the skin associated with various affections of the central nervous system, or of the sympathetic or of the ductless glands, and the part which relates in their genesis to disturbances of nutrition in general and the endocrine system and the sympathetic in particular."<sup>114</sup>

## 2. Endocrino-sympathetic Syndromes

I will only retain from among the above-mentioned syndromes exophthalmic goiter, Addison's syndrome, scleroderma and diabetes mellitus by reason of their double interest, which is both doctrinal and practical, and of the large number of studies that they have occasioned, and are still causing every day.

### (1) BASEDOW'S SYNDROME

I have nothing to say concerning the immense bibliography of exophthalmic goiter, for which I refer you to Biedl's work on the subject and the recent report of Roussy at the Congress of Luxembourg (August, 1914). I will simply state that instead of taking sides for the thyroïdal theory whose last favorable pleading was sustained with excellent arguments by Roussy and Clunet,<sup>115</sup> or for the sympathetic theory defended by Gley and Cleret,<sup>116</sup> with the aid of arguments drawn from experimental and anatomo-clinical facts, one<sup>117</sup> of which is personal to myself, I prefer to say that it is the same with Basedow's syndrome as with all the endocrino-sympathetic syndromes, that they are all the expressions of a disturbance of function, and that this function is disordered as well by a glandular lesion as by a disturbance of its nervous regulating mechanism.

From a physiological viewpoint I reiterate, therefore, the unity of the Basedovian syndrome in its divers clinical modalities.<sup>118</sup>

The cases due to thyroïdal lesions are certain. I argue no more. The cases due to nervous disorders appear no less often.

Curschmann<sup>119</sup> has seen in a woman tabetic an intermittent Base-

<sup>114</sup> Laignel-Lavastine et Viard, *Adipose segmentaire des membres inférieure*, Soc. de Neurol., 11 juill., 1912; *Nouv. Iconographie de la Salpêtrière*, 1912, No. 6.

<sup>115</sup> G. Roussy et J. Clunet, *Les lésions du Corps thyroïde dans la maladie de Basedow*, *Annales de médecine*, t. 1, No. 4, avril, 1914, pp. 395-438.

<sup>116</sup> E. Gley et Cleret, *Recherches sur la pathogénie du goitre exophthalmique*, *J. de Physiol. et de Pathol. gén.*, 1911, p. 928, et Cleret, *Thèse*, 1912.

<sup>117</sup> Laignel-Lavastine et Bloch, *Syndrome de Basedow chez une tuberculeuse*, *Arch. gén. de médecine*, sept., 1904, pp. 2456-61.

<sup>118</sup> L'épreuve de l'hypophyse (ralentissement du pouls chez les Basedowiens, découverte par Claude et ses élèves (Soc. de médecine des hôp., 19 juin, 1914) permet de limiter, dans le même esprit, le syndrome de Basedow.

<sup>119</sup> Curschmann, *Sur des symptômes basedowiens intermittents (dans les tabes et l'asthme bronchique)*. *Zeitschrift f. klinische Medizin*, 1912, LXXVI, 3-4.

dovian syndrome coincident with gastric crises. He saw in this a sympathicotonic sign, and he was not far from siding with the opinion of Morat and Abadie, who saw in the lesion of the thoracic sympathetic the starting point of the Basedovian syndrome.

The beneficial influence exercised by adrenalin on the crises is to be noted.

This fact is contrary to the theory of Gottlieb-O'Connor, according to which the thyroïdal secretion sensitizes the terminal organs of the sympathetic.

It is explained on the other hand by the researches of Elliot and Durham, who established the fact that after an injection of adrenalin excitation of the splanchnic nerve caused a lowering of the blood pressure instead of the normal elevation, and this exists also in gastric crises.

Being more synthetic than analytic, looking at things physiologically and not anatomically or etiologically, I conclude that the Basedovian syndrome in its fundamental mechanism is an endocrino-sympathetic syndrome, whose divers clinical types arise from various lesions, at times endocrinal (always thyroïdal, sometimes thymic, ovarian, parathyroïdal, etc.), at others nervous (cervical or bulbar sympathetic) under the dominance of intoxications or infections acute or chronic, either general or local, of which the most frequent are acute articular rheumatism and tuberculosis.

## (2) ADDISON'S SYNDROME

Thus from a case of Addison's syndrome without appreciable gross lesions of the suprarenals (1899) I wrote my thesis<sup>120</sup> in an endeavor to demonstrate that there were Addisonians in whom nothing was to be seen except lesions of the sympathetic, in whom the suprarenal disturbances were secondary to nervous changes, and who showed all the intermediary signs of the melanodermic<sup>121</sup> tuberculosis. To the anatomical theory of the Addisonian discoloration I put in opposition a more comprehensive physiological theory and to the lesional contingency the functional necessity.

The recent observation of N. Pende and Varvaro<sup>122</sup> came to the support of this point of view. They have seen in a man of thirty-six years of age an Addisonian syndrome secondary to a rapid pulmonary tuberculosis. At autopsy the suprarenals were normal in their make-up. In the cortex the spongiocytes were rare, and pigment was almost completely lacking in the reticular zone.

<sup>120</sup> Laignel-Lavastine, *Recherches sur le plexus solaire*, Thèse, 1903, p. 420.

<sup>121</sup> Laignel-Lavastine, *La mélanodermie des tuberculeux*, Soc. méd. des hôp., 29 janv., 1904, et *Arch. gén. de méd.*, oct., 1904, pp. 2497-2520.

At the level of the solar plexus there were two aberrant suprarenals of normal structure. The ganglia of the solar plexus were free from tuberculous lesions, but they were of notable size, and examined histologically they appeared poor in sympathetic nerve cells and rich in new-formed connective tissue. The nervous elements still seen presented pigmentary atrophy.

To-day one differentiates the primitive Addisonian syndrome of slow and progressive evolution from the secondary Addisonian syndrome, which is seen in the already more or less advanced tuberculous cases, and which has a less clearly defined symptomatology.

Pende and Varvaro think that in the first case the anatomical substratum has its seat in the suprarenal, and in the second in the region of the solar plexus. Their reported case is a type of the secondary Addisonian syndrome.

Porak and myself have observed a case which anatomico-clinically was quite similar.

Thinking physiologically<sup>123</sup> one can conclude that the Addisonian syndrome is the expression of a certain degree of chronic suprarenal insufficiency with a disturbance of adreno-sympathetic pigmentary regulation.

In this adreno-sympathetic syndrome one can differentiate two anatomico-clinical forms: one form with predominance of the suprarenal lesions, it is the most frequent, and in general is clinically primitive, the second form with predominance of the sympathetic, periadrenal, solar or splanchnic lesions. It is less frequent, often fruste, and in general is clinically secondary to a pulmonary pthisis.

### (3) SCLERODERMA

The absence of the thyroïdal sign of Vincent in acute articular rheumatisms followed at first by Basedow's syndrome, and later on by evidences of thyroïdal atrophy with the appearance of scleroderma, which sometimes is apparently arrested by thyroïdal medication, has caused a belief in the existence of a scleroderma due to thyroïdal disturbances of rheumatic origin.

This endocrinogenic form of scleroderma is not to be questioned. It is quite possible that it is not the only one, and that other

<sup>122</sup> N. Pende et Varvaro (de Palermo), *Maladie d'Addison avec intégrité apparente des glandes surrénales et avec hypertrophie des glandes surrénales accessoires*, *La Riforma medica*, Nos. 40 et 41, 4 et 11 oct., 1913, pp. 1093 et 1124.

<sup>123</sup> La communication récente de Hirtz and Debre (*Addisonien observe en 1902 considère comme guéri, retrouve en 1913, autopsie*), a la Soc. med. des hop., le 26 juin, 1914, et la discussion que suivit entre L. Bernard, Netter et Sergent (3 juillet, 1914, p. 20), ne contredisent pas mes conclusions.—Voir de plus Fayolle, Thèse, 2 juillet, 1914.

endocrinal disturbances are capable of producing scleroderma or add their action to that of the thyroid<sup>124</sup> in its causation.

In addition, in spite of Touchard,<sup>125</sup> it seems very difficult to do away with a sympathetic factor in certain cases.

Referring to an association of Basedow's syndrome and scleroderma, G. Marinesco and Goldstein<sup>126</sup> say that it is "evident that the sclerodermic syndrome does not depend entirely on a disturbance of thyroidal function, but that this disturbance exercises a certain action on the sympathetic system, and brings about in this way the appearance of the scleroderma." There are cases, as they say, which confirm all the pathogenetic theories: the trophoneurotic, the angio-trophoneurotic, the sympathetic, the vascular, the pituitary, the thyroidal and the pluriglandular. However none of these theories can be applied to these cases as a whole.

Gauthier<sup>127</sup> distinguishes two forms of scleroderma, the ordinary, depending upon hyperthyroidism, and a special type, with a less parchment-like skin and having subcutaneous fat, depending upon hypothyroidism.

Cassirer<sup>128</sup> puts in the list of the vegetative syndromes the vasomotor and trophic neurosis, among which he classifies scleroderma.

Marinesco and Goldstein consider that the thyroidal secretion acts in the cases accompanied by Basedovian symptoms, as well as in those with other thyroidal manifestations, through the sympathicotrope action of that secretion.

The connections and even the associations of certain sclerodermas with Basedovian and Addisonian syndromes compel me to admit that if in the first place scleroderma is an endocrinal syndrome, it is also sometimes a vegetative syndrome, and that consequently it has the right to be quoted among the group of endocrino-sympathetic syndromes.

#### (4) DIABETES MELLITUS

Diabetes arises from a disorder in the regulating mechanism of the sugar function. Glycosuria, the most frequent disorder of this function, is at first heading an endocrino-sympathetic syndrome.

<sup>124</sup> Voir à l'appui: Laignel-Lavastine, *Sclérodémie mélanodermique*, Soc. med. des hôp., 31 janvier, 1908; Dupré et P. Kahn, *Sclérodémie et mal. de Raynaud*, Soc. méd. des hôp., 11 juin, 1909; Chantemesse et Coureux, *Sclérodémie avec atrophie thyroïdienne et mélanodermie*, Soc. méd. des hôp., 3 juill., 1914.

<sup>125</sup> Touchard, Thèse, 1906.

<sup>126</sup> Marinesco et Goldstein, *Syndrome de Basedow et Sclérodémie*, *Nouv. Iconographie de la Salp.*, juill.-août., 1913, pp. 272-290.

<sup>127</sup> Ch. Gauthier, *Fonct. du corps thyroïde*, R. de Méd., 1900, p. 442.

<sup>128</sup> Cassirer, *Die vasomotorisch-trophischen Neurosen*, 2<sup>e</sup> ed., 1912, pp. 536-700.

Without going into the secretion of sugar by the liver, which was the first internal secretion known, or into the influence of the internal secretions of the pancreas on sugar metabolism, it suffices to mention adrenalin glycosuria as well as suprarenal diabetes to show the existence of glycosuria of endocrinal origin.

In addition McLeod, after Cavazzini, has laid stress on the glycosuria following excitation of the great splanchnic and on the fact that puncture of the bulb in the normal dog is without effect after section of the splanchnic nerves.

There is need therefore of a sympathetic factor in the production of certain glycosurias.

Finally in the decapsulated dog puncture of the fourth ventricle (Mayer), as well as stimulation of the splanchnic (Gautrelet and Thomas), does not produce glycosuria. This proves the need of a double endocrino-sympathetic factor in certain glycosurias.

One can conceive, therefore, the possibility of diabetic cases, endocrino-sympathetic syndromes, in which sometimes either the endocrinal factor or the sympathetic factor seems to predominate.

### 3. Psycho-neuroses

I indicated in 1908 the importance of endocrine disorders in the psycho-neuroses. Facts published since then in the literature and my personal practice have confirmed me in my opinion. One part of functional neurology comes under the heading of endocrino-neurology to-day.

This subject will be found worthy of great elucidation. I can not go into it here, and will say but a word regarding endocrine disorders among the "nervous," the neurasthenics, the hysterics, the psychasthenics and the epileptics.

#### (I) NERVOUSNESS

It will be interesting clinically, said I in 1908, not to stop at a simple semiologic diagnosis in the presence of a neurosis, but to inquire into the reasons for the irritable weakness of the nervous system in the general functioning of the organism, and from this point of view not to neglect the examination of the internal secretions.

The Viennese School, especially Eppinger and Hess,<sup>129</sup> in the neurosis of Oppenheim, have distinguished the two clinical types of vagotonics and sympathicotomics, the relationships of which they

<sup>129</sup> H. Eppinger et L. Hess, *Die Vagotonie, Sammlung klinischer Abhandlungen über Pathol. u. Therap. der Stoffwechsel u. Ernährungsstörungen*, f. 9-10, Berlin, 1910. Tr. Kraus and Jelliffe, *Neurological Monographs*.



have striven to connect with such and such disturbances of internal secretion. Their remarkable description of vagotonics, which is classic to-day, has been translated or recapitulated in all languages. I refer you to these works.<sup>130</sup>

Before that Léopold Lévi and H. de Rothschild<sup>131</sup> had prepared the way with their excellent study on thyroidal neuroses.

In a number of cases the clinical types of neuroses, such as the vaso-motor habitus of Savini<sup>132</sup> or the emotional constitution of Dupré,<sup>133</sup> come under the heading of thyroidal neuroses, and from a diagnostic standpoint the joining of a simple clinical type to an endocrino-nervous syndrome is a step forward, because one enters a little further into the understanding of the morbid mechanism.

Moreover a good many vagotonics, like a good many sympathicotonics, also come under the heading of dyshyperthyroidal neuroses, and these different effects arising from the same endocrine disorder—supposing that it always is the same—should not cause amazement.

They are on the same order as the facts which were noted by Asher and de Rodt<sup>134</sup> in their experiments on the thyroidal secretions. According to the individual peculiarities of the animals, it was sometimes the action on the vagus and sometimes the action on the sympathetic that predominated. In addition the effect of an injection of thyroidal extracts depended in great measure on the degree of excitability of the nerves of the animal experimented upon.

This observation seemed to me as being of extreme importance and of a general application. In pointing out more or less marked reactional phenomena in the nervous system as being hand in hand with certain secretions with which they are for the moment more or less in accord, evidence is given of the dangers of too hasty inductions relative to the action of the endocrine secretions on the separate parts of the nervous system and to their specific elective action, which are to a certain extent antagonistic.

There are not only thyroidal neuroses allied with all the modalities of stimulation or insufficiency of thyroidal secretion, but dis-

<sup>130</sup> Cheinisse, *Sem. méd.*, 20 nov., 1912, pp. 553-556; W. M. Kraus et S. E. Jelliffe, *J. OF NERV. AND MENT. DISEASE*, mars, avril, mai, 1914, p. 164.

<sup>131</sup> Léopold Lévi et H. de Rothschild, *Etude sur le corps thyroïdien*.

<sup>132</sup> E. Savini, *Le type constitutionnel sympathique ou vaso-motor*, *Progrès médical*, 15 fév., 1913, pp. 82-85.

<sup>133</sup> E. Dupré, *La constitution émotive*, *Paris méd.*, 7 oct., 1911, p. 404.

<sup>134</sup> L. Asher et M. de Rodt, *Innervat. des gl. à secrét. int. et act. des produits de secrét. int. sur le syst. nerv.*, *Soc. suisse de Neurol.*, 11-12 nov., 1911.

*Rev. méd. de la Suisse romande*, XXXII, No. 2, p. 183, 20 fév., 1912.

turbances of the ovaries, testicles, suprarenals and the pituitary may be the origin of beginning neuroses.

This idea of an attempt to discover the endocrinal disturbance before the neurosis becomes sufficiently marked to be morbid allows one perhaps to restore an equilibrium to these nervous temperaments through an organotherapy, which is to a certain extent prophylactic.

They are helped in this way before, to use a vulgarism, they have had a chance to get the habit of the disease.

Finally among "the nervous" endocrine disorders may be in their turn secondary to nervous disturbances. These secondary neurogenous endocrinal symptoms must not be confounded with primitive endocrine disorders—the causes of the nervous disorders. This intricacy is common among the hyposphyxics of Martinet; I have under observation at the present time a nervous woman with hyposphyxia and hypothyroidism, whose extremely low arterial tension is improved more by small doses of thyroid than by suprarenal, and I believe that it is through a nervous influence that the thyroïdal insufficiency of scarlatinal origin reacts upon the suprarenal.

After what I have said concerning endocrinogenic asthenias I will be very brief as regards neurasthenia of endocrinal origin. Since attaching the importance to it that I did in 1908, I have searched for it regularly in my practice, and have often found it. The forms connected with adrenal and genital insufficiency (diastematic and prostatic) seem to me to predominate in the male, and the forms connected with ovarian and thyroïdal<sup>135</sup> insufficiency to predominate in the female. Certain neurasthenias of infectious origin, such as the tuberculous, syphilitic, and gonorrheal, result as much if not more from the endocrinal insufficiency caused by the microbes than from the toxines produced by them directly.

These endocrine disorders which cause neurasthenia must not be confounded with the secondary neurogenous endocrinal symptoms, which are often seen in neurasthenias, and which bear mostly on the vegetative nervous system.

The two disorders—endocrinogenic neurotic and neurogenic endocrinal—often coexist, and by their intricacy complicate the clinical picture. The analysis can be gotten at through the therapeutic results.

<sup>135</sup> Allen Starr, Neuroses depend upon errors of inter. secret. of the ductless glands, *Med. Record*, 20 juin, 1912.

### (3) HYSTERIA

Hysteria, whatever the idea may be that one holds in regard to it,<sup>136</sup> is observed among "the nervous."

I have shown the frequency of neuroses of endocrinal origin. I believe that I can class the disorders of internal secretion among the predisposing causes of hysteria through the intermediary of nervosity. As a matter of fact I have often found endocrinal disturbances, especially of the thyroïdal or ovarian type, among hysterics.

### (4) PSYCHASTHENIA<sup>137</sup>

Etymologically psychasthenics should be classed among the neurasthenics in whom the asthenia bears especially on the psychic sphere.

But following along with Raymond and Janet we class especially as psychasthenics those who, on the whole, are obsessed.

When one follows these cases one sees that their paroxysmal blustering syndromes are nothing but the morbid offshoots of deeper variations of nervous tonus or psychic tone. These changes in women are nearly always connected with the sexual life. In man one finds them running parallel with such symptoms as headache, insomnia, hyper- or hypotension, tachycardia and constipation, which frequently can be connected with endocrinal disorders.

Thus among the predisposed, obsessions, which might be regarded as a mental autonomic syndrome, are often nothing but the psychic expression of a more or less diffuse anxiety which in itself is the result of a disturbance of the sympathetic system of endocrinal origin. Thyroïdal excitation particularly, by increasing the irritability of the peripheral sympathetic centers which it controls, predisposes to these dissociations of personality. The thyroid, so to speak, is an anarchistic emancipator.

Be that as it may, the variations in nervous and psychic tone thus determined may react secondarily on all the vegetative functions not forgetting the ductless glands, and can thus establish a vicious circle.

### (5) EPILEPSY

It is always wise in the diagnosis of an epilepsy after becoming advised as to the causes explaining the cortical changes to pass in

<sup>136</sup> Laignel-Lavastine, *Les réactions anti-sociales des hystériques*, Paris Médical, 30 mai, 1914.

<sup>137</sup> Schnyder, L., *R. méd. de Suisse romande*, oct., 1913; Lubetzki, S., *R. de méd.*, août, 1913.

review the reasons for the organic poisoning and among these not to overlook the glandular disturbances. The search for the minute signs of these disturbances may thus institute the use of one glandular therapy rather than another. It is most often the thyroidal disturbances that are revealed in endocrinal disorders among epileptics.

Many subsequent works<sup>138</sup> have confirmed this conclusion in my report of 1908.

Sometimes they are hypothyroïdeale in type and sometimes dyshyperthyroïdeale. This is not contradictory. The endocrinal disorder, according to the statement of Léopold Lévi, "is the pathological mordant that sensitizes centers already predisposed." The endocrinolepsy,<sup>139</sup> whatever form the crisis may take, is set free by a complete rupture of the endocrinal equilibrium. The incidental causes alone are different. Thus in a still unpublished lecture<sup>140</sup> on the thyroid body and epilepsy pertaining to a confusional epileptic stupor seen in a tuberculous heredo-alcoholic Basedovion, I showed that the crisis coincided with and followed her menstrual periods, while with her hypothyroïdal sister they preceded them as a rule, and were absent during pregnancy.

In the epileptic seizures of thyroidal origin, therefore, I wish to differentiate the dyshypothyroïdeale crises from the dyshyperthyroïdeale<sup>141</sup> crises; these latter discharges moreover possibly surviving in all three forms of thyroidal instability.

#### 4. TEMPERAMENTS

Temperament, as I said at Dijon in 1908, is the dynamic characteristic of the organism, just as constitution is the static characteristic. Following this conception of Professors Bouchard, Landouzy and Roger it can be stated that what one is to physiology the other is to anatomy. Now it appears to me that among the various func-

<sup>138</sup> Sicard, Journ. de med. de Paris, 1912; Gelma, Rev. de med., 10 janv., 1913, pp. 26-39. Guilton, Contrib. à l'ét des symp. épileptiques dans les états thyroïdiens, Th., Montpellier, 1913, No. 58; Enzière et Margarot, Soc. de sc. méd. de Montpellier, 2 mai, 1913; Silvestri, Opothérapie surréno-médull. et épilepsie, Il Policlinico, 29 juin, 1913, pp. 917-922; Dufour et Legros, Syndrome hypo-ovarien et hypo-thyroidien. Crises épileptiformes (vagotonie), Soc. méd. des hôp., 27 mars, 1914; Bolten G., Monatsch. f. Psych. u. Neurol., 33, No. 2, fév., 1913; Claude et Schmieregeld, Encéph., 10 janv., 1909.

<sup>139</sup> Léopold Lévi, Les endocrinolepsies, Soc. de méd. de Paris, 9 janv., 1914, p. 44.

<sup>140</sup> Laignel-Lavastine, Clinique psychiatrique, 22 mars, 1914.

<sup>141</sup> Ces crises me paraissent vraiment rythmées par les règles quoi qu'en disent Toulouse et Marchand (R. de Psychiatrie, mai, 1913).

tions, the individual varieties of which have to do with temperaments, those of the internal secretions should not be neglected, and when one decides to take up the long-forsaken study of temperaments in accordance with the classical types—the sanguinary, the nervous, the lymphatic and the bilious, one might discern perhaps the thyroïdal, the pituitary, the adrenal, the ovarian and diasthematic, etc.

This view of the question is but the application to the internal secretions in relation to temperament, of the masterly conception of Prof. Charles Richet expressed at the Congress of Vienna in 1910: "We are as yet but at the portal of that chemistry of the imponderable, founded on the analysis of biological functions, and although we can already foresee some of the results, we are soon led into a region in the study of the physiology of the individual, which until to-day was almost unexplored," that physiology which, in my lecture at the opening of the course on medico-legal psychiatry in 1910, I called the differential psychology, and I linked differential psychology with the knowledge of character and differential anatomy with the knowledge of constitution.

Since then the idea has been greatly amplified, and Prof. N. Pendé<sup>143</sup> has allotted a chapter to it in his remarkable report of 1912 on the internal secretions. As a clever clinician he has related the constitutional vascular hypotonia of Ferrannini with the thymo-lymphatic state of Paltauf or the asthenic or hypoplastic constitutional state characterized by hypoplasia of chromaffin and genital tissue combined with hyperplasia of lymphatic and thymic tissue.

Then again he believes that he can connect the vagotonia of Eppinger and Hess with the exudative diathesis of Czerny.

He considers the lymphatic and thymo-lymphatic states to which he adjoins the chlorotic state as an organic immaturity of the endocrinal system in its chromaffin and genital parts contrasting with excessive development in the same system of its lymphatic and thymic parts. He recalls the antithesis established by Viola between the apoplectic or short or megalosplanchnic habitus with the phthisical or long or microsplanchnic habitus. He adds that very frequently hypothyroïdeia coincides with the megalosplanchnic habitus and hyperthyroïdeia with the microsplanchnic. Remarking also that

<sup>142</sup> Rapin, *Angioneuroses familiales*, R. med. de la Suisse romande, 1907, p. 196.—G. Maranon, R. de med., mars, 1914, p. 180.—Falta, loc. cit., p. 39.—Léopold Lévi, *Familles thyroïdiennes et dysendocriniennes*.

<sup>143</sup> N. Pendé, *Le secrezioni interne nei rapporti con la clinica XXII\** Congresso di Medicina Interna in Roma, oct., 1912.

he has often seen signs of vagotonia among the megalosplanchnics and of sympathicotonia among microsplanchnics he deducts this double equation: vagotonia-megalosplanchnia-hypothyroidea; sympathicotonia-microsplanchnia-hyperthyroidea.

Pendé very prudently does not advance these considerations except as a means of indicating the road to follow, and in fact this classification seems to me to err through too great a desire for symmetry and by too static a conception of the notions regarding vagotonia and sympathicotonia.

These predominances as a rule only express the evolutionary moments of the individual. Thus when asleep at night we are all vagotonics. The adult and the aged differ more from the child than the sleeping man from the awakened. Their vegetative nervous formula has therefore the chance of not remaining the same all during life.

If I criticize the too sharply drawn lines of the theoretical elucidation I share, as I have already said, in the directing idea. It is moreover essentially French. Léopold Lévi and H. de Rothschild have been the first to deserve the credit for connecting the classical neuro-arthritic diathesis with hyperthyroidism.<sup>144</sup> It is true that prior to that time Hertoghe classed adenoid cases as among the hypothyroidal, and opened the way for the classification of many lymphatic temperaments among cases of hypothyroidism.

Another step along the trail brings us to the diatheses of Bazin—a masterly conception and a very true one, which the fancies of the pastoral era had caused to be forgotten, but to which we bring back the analysis of temperament in the light of endocrinology.

Finally I must recall that Lancereaux, when he saw in the sympathetic the principal factor in herpetism, had in advance the intuition of the ties which unite endocrino-sympathetic disturbances with temperaments.

To-day I believe it possible to enlarge and clarify the question a little, thanks to what I have called, in a clinical lecture, the endocrino-diagnosis of temperaments; an endocrino-diagnosis which must be worked out according to the method of glandular tests of Claude and his pupils, and which will allow one to depict a series of types. This series of types will depend on thyroidal or ovarian or testicular or pituitary or suprarenal temperaments more or less clearly defined, according to the more or less marked predominance of one or of several of the glands of internal secretion in the endo-

<sup>144</sup> Léopold Lévi, *Neuro-arthritis et gl. endocrines*, *Mouv. méd.*, mai, 1913.

crinal equilibrium. I expect to publish in the near future a description along these lines of the principal temperaments.

### 5. CHARACTER<sup>145</sup>

Character, to my mind, as I said in 1908, is nothing but the psychological expression of temperament. Constitution, temperament, character are thus but three expressions—anatomical, physiological and psychological—of the reactional coefficient of the individual.

“The importance of individual varieties of internal secretions will be seen again therefore in characters. The laity have long spoken of good or bad humor in their spontaneous psychology and also of humor in medical parlance. This identity of terminology seems to me to conceal a profound meaning, which the study of the internal secretions uncovers. These secretions by their variations react on the mental life as well as on the rest of the organism, and manifest themselves at first and above all by changes of humor, modifications of affective life, because the latter rather than motor or especially intellectual activity depends on organic life from which it can scarcely be separated.

For a long time my observations have done nothing but confirm me in my opinions. The choleric are such only through the thyroidal temperament, just as the lazy are such only through suprarenal hypoplasia.

Nevertheless, even if an endocrinal factor often enters into the formation of character, I do not claim that it always does so, and many other elements play a primordial rôle in such formation. In addition the law of constancy allows the establishment of relationships between morphological and psychological series which are by no means causal. This is what Bergson has caught a glimpse of in his *Creative Evolution*, when he says that each physiological disposition is a necessary but not a sufficient condition for each psychic state, and that it is possible to have many psychic states from the same physiological state of the cerebral gray matter.

### CONCLUSIONS

1. From a morphological standpoint there exist clearly defined connections between the nervous system and certain glands of internal secretion, especially between the sympathetic and the chromaffin systems.

<sup>145</sup> Kollarits Jenő, *Charakter und Nervosität*, Budapest, 1912.

2. From a physiological standpoint experimentation has shown that stimulation or predetermined sections of the central or peripheral nervous system modify certain internal secretions and conversely that changes produced in these secretions or the injection of their hormones, where such are known and isolated, modify the nervous functions, particularly the excitability of the vegetative system, with predilection sometimes for the autonomic and sometimes for the sympathetic. The School of Vienna deserves the credit for having shown the importance of these elective relations.

3. From a pathological standpoint much less is known as yet than one would suppose. The truth of the endocrino-nervous relationships should not be admitted without a critical analysis bristling with facts. Nevertheless it can be said that

1. Nervous disorders exist due to disturbances of internal secretion, and disturbances of internal secretion exist due to nervous disorders.

#### ENDOCRINO-NERVOUS RELATIONSHIPS

A. Coincidence.

B. Association. { 1. Proximate.  
2. Mediate.

C. Causality.

- |              |   |                                    |   |  |
|--------------|---|------------------------------------|---|--|
| 1. Simple... | { | 1° Endocrino-nervous.              | { | 1. Morphological evolutionary.<br>2. Morphological humoral.<br>3. Physiological humoral.<br>4. Physiological nervous.<br>5. Psychological. |
|              |   | (1) Direct.                        |   |  |
|              |   | (2) Indirect through intermediary. |   |  |
|              |   | 2° Neuro-endocrine.                |   |  |
|              | { | (1) Direct.                        | { | 1. Morphological evolutionary.<br>2. Physiological reflex.<br>3. Psychological.<br>4. Motor activity.<br>5. General nutrition.             |
|              |   | (2) Indirect through intermediary. |   |  |
|              |   | 3° Endocrino-neuro-endocrine.      |   |  |
|              |   | 4° Neuro-endocrino-nervous.        |   |  |

2. The two-fold critical analysis of the neurological and particularly the endocrinological methods of investigation permits, in the midst of the unknown, the redemption of certain definite relationships between the endocrinal and the nervous disorders.

3. Until more ample investigation it seems to me that these relationships might be expressed in the following table.

In practice the great aid that endocrinology brings to the study of neurology and especially functional neurology manifests itself particularly in the clinical study of



1. Ordinary symptoms, such as asthenia, headaches, insomnia, anxiety, sweats, constipation, arterial hypertension and obesity.
2. Endocrino-sympathetic syndromes, such as Basedow's syndrome, Addison's syndrome, scleroderma and diabetes mellitus.
3. Psycho-neuroses.
4. Temperaments.
5. Characters.

Endocrino-diagnosis of temperaments, particularly through glandular tests and sympathico-vago-tonic examinations, in penetrating the familial heredity, will allow us to use prophylactic measures in combating diatheses and in combating certain of the factors, the humoral and neuro-vegetative factors for instance, which are formative of character.

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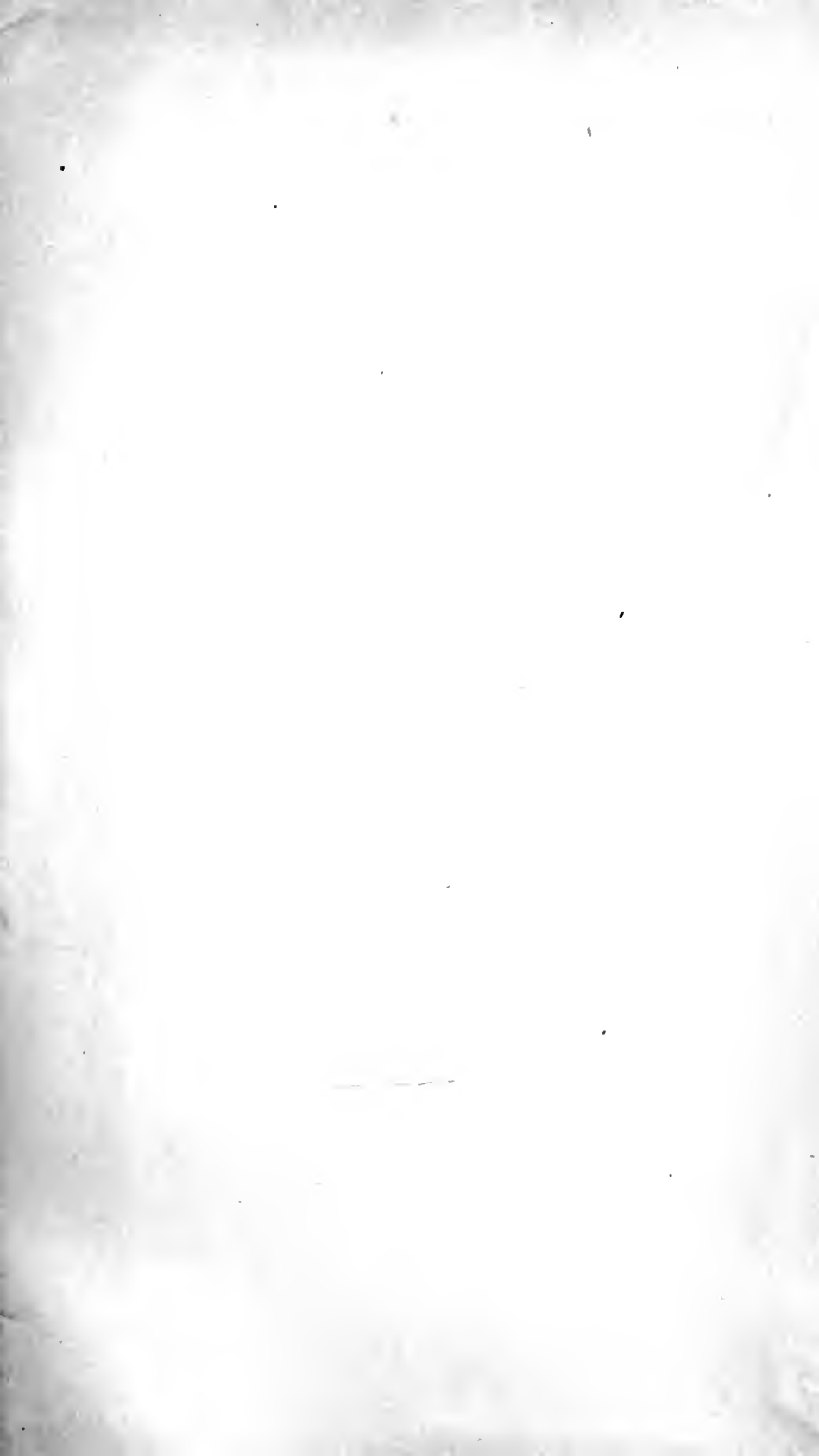
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